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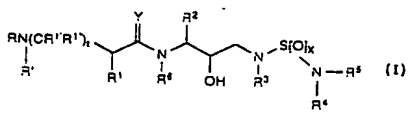
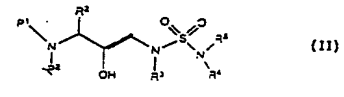
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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/US93/10552</p> <p>(22) International Filing Date: 29 October 1993 (29.10.93)</p> <p>(30) Priority data: 07/968,730 30 October 1992 (30.10.92) US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US Filed on 07/968,730 (CON) 30 October 1992 (30.10.92)</p> <p>(71) Applicants (for all designated States except US): G.D. SEARLE &amp; CO. [US/US]; Corporate Patent dept., P.O. Box 5110, Chicago, IL 60680-5110 (US); THE MONSANTO COMPANY [US/US]; 800 North Lindsbergh Boulevard, St. Louis, MO 63166 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): VAZQUEZ, Michael, L. [US/US]; 233 Saratoga Court, Gurnee, IL 60031 (US); MUELLER, Richard, A. [US/US]; 562 Stonegate Terrace, Glencoe, IL 60022 (US); TALLEY, John, J. [US/US]; 1510 Amisk Court, Chesterfield, MO 63017 (US); GETMAN, Daniel, P. [US/US]; 66 Sunnyhill Court, Chesterfield, MO 63017 (US); DECRESCENZO, Gary, A. [US/US]; 536 Schrader Farm Drive, St. Peters, MO 63376 (US); SUN, Eric, T. [US/US]; 7614 Palmilla Drive, Apartment 58, San Diego, CA 92122 (US).</p>	<p>(74) Agents: UNGEMACH, Frank, S. et al.; G.D. Searle &amp; Co., Corporate Patent dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).</p> <p>(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>	
<p>(54) Title: HYDROXYETHYLAMINO SULFAMIC ACID DERIVATIVES USEFUL AS RETROVIRAL PROTEASE INHIBITORS</p>		
<p>(57) Abstract</p> <p>Hydroxyaminoethyl sulphamic acid compounds of formulae (I) and (II), wherein <math>R</math>, <math>R'</math>, <math>R^1</math>, <math>R^{1'}</math>, <math>R^2</math>, <math>R^3</math>, <math>R^4</math>, <math>R^5</math>, <math>R^6</math>, <math>x</math>, <math>t</math>, <math>Y</math>, <math>P^1</math> and <math>P^2</math> are as defined in Claims 1 and 97, are effective as retroviral protease inhibitors, and in particular as inhibitors of HIV protease.</p> <div style="text-align: right;">  <p>(I)</p> </div> <div style="text-align: right;">  <p>(II)</p> </div>		

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HYDROXYETHYLAMINO SULFAMIC ACID DERIVATIVES USEFUL AS RETROVIRAL  
PROTEASE INHIBITORSBACKGROUND OF THE INVENTION

5

1. Field of the Invention

The present invention relates to retroviral protease inhibitors and, more particularly, relates to novel compounds and a composition and method for  
10 inhibiting retroviral proteases. This invention, in particular, relates to sulfamic acid derivatives of hydroxyethylamine protease inhibitor compounds, a composition and method for inhibiting retroviral proteases such as human immunodeficiency virus (HIV)  
15 protease and for treating a retroviral infection, e.g., an HIV infection. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

20 2. Related Art

During the replication cycle of retroviruses, gag and gag-pol gene products are translated as proteins. These proteins are subsequently processed by a virally encoded protease (or proteinase) to yield viral enzymes  
25 and structural proteins of the virus core. Most commonly, the gag precursor proteins are processed into the core proteins and the pol precursor proteins are processed into the viral enzymes, e.g., reverse transcriptase and retroviral protease. It has been shown  
30 that correct processing of the precursor proteins by the retroviral protease is necessary for assembly of infectious virions. For example, it has been shown that frameshift mutations in the protease region of the pol gene of HIV prevents processing of the gag precursor  
35 protein. It has also been shown through site-directed

mutagenesis of an aspartic acid residue in the HIV protease that processing of the gag precursor protein is prevented. Thus, attempts have been made to inhibit viral replication by inhibiting the action of retroviral proteases.

Retroviral protease inhibition may involve a transition-state mimetic whereby the retroviral protease is exposed to a mimetic compound which binds to the enzyme in competition with the gag and gag-pol proteins to thereby inhibit replication of structural proteins and, more importantly, the retroviral protease itself. In this manner, retroviral replication proteases can be effectively inhibited.

Several classes of compounds have been proposed, particularly for inhibition of proteases, such as for inhibition of HIV protease. Such compounds include hydroxyethylamine isosteres and reduced amide isosteres. See, for example, EP O 346 847; EP O 342,541; Roberts et al, "Rational Design of Peptide-Based Proteinase Inhibitors, "Science, 248, 358 (1990); and Erickson et al, "Design Activity, and 2.8Å Crystal Structure of a C<sub>2</sub> Symmetric Inhibitor Complexed to HIV-1 Protease," Science, 249, 527 (1990).

Several classes of compounds are known to be useful as inhibitors of the proteolytic enzyme renin. See, for example, U.S. No. 4,599,198; U.K. 2,184,730; G.B. 2,209,752; EP O 264 795; G.B. 2,200,115 and U.S. SIR H725. Of these, G.B. 2,200,115, GB 2,209,752, EP O 264,795, U.S. SIR H725 and U.S. 4,599,198 disclose urea-containing hydroxyethylamine renin inhibitors. G.B. 2,200,115 also discloses sulfamic acid-containing hydroxyethylamine renin inhibitors, and EP 0264 795 discloses certain sulfamic acid-containing

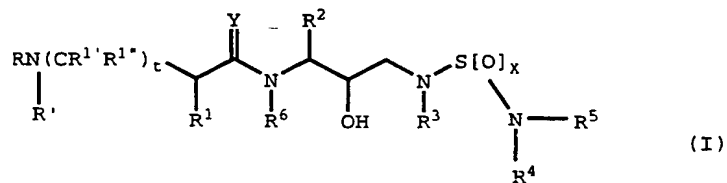
hydroxyethylamine renin inhibitors. However, it is known that, although renin and HIV proteases are both classified as aspartyl proteases, compounds which are effective renin inhibitors generally cannot be predicted to be effective HIV protease inhibitors.

#### BRIEF DESCRIPTION OF THE INVENTION

The present invention is directed to virus inhibiting compounds and compositions. More particularly, the present invention is directed to retroviral protease inhibiting compounds and compositions, to a method of inhibiting retroviral proteases, to processes for preparing the compounds and to intermediates useful in such processes. The subject compounds are characterized as sulfamic acid derivatives of hydroxyethylamine inhibitor compounds.

#### DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a retroviral protease inhibiting compound of the formula:



or a pharmaceutically acceptable salt, prodrug or ester thereof wherein:

R represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, alkoxy carbonyl, aryloxyalkyl, heteroaryloxyalkyl, aralkoxy carbonyl, alkyl carbonyl, cycloalkyl carbonyl, cycloalkyl alkoxy carbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxy carbonyl, aryloxy carbonyl alkyl, aryloxyalkanoyl, heterocyclyl carbonyl, heterocycliloxy carbonyl, heterocyclylalkanoyl, heterocyclyl alkoxy carbonyl, heteroaralkanoyl, heteroaralkoxy carbonyl, heteroaryloxy carbonyl, heteroaroyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals, or wherein said aminocarbonyl and aminoalkanoyl radicals are disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen, radicals as defined for R<sup>3</sup> or R"SO<sub>2</sub>- wherein R" represents radicals as defined for R<sup>3</sup>; or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radicals;

R<sup>1</sup> represents hydrogen, -CH<sub>2</sub>SO<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -CH<sub>2</sub>C(O)NHCH<sub>3</sub>, -C(CH<sub>3</sub>)<sub>2</sub>(SH), -C(CH<sub>3</sub>)<sub>2</sub>(SCH<sub>3</sub>), -C(CH<sub>3</sub>)<sub>2</sub>(SC<sub>6</sub>H<sub>5</sub>), -C(CH<sub>3</sub>)<sub>2</sub>(S[O]CH<sub>3</sub>), -C(CH<sub>3</sub>)<sub>2</sub>(S[O]<sub>2</sub>CH<sub>3</sub>), alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine and methionine and the sulfoxide (SO) and sulfone (SO<sub>2</sub>) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine,

glutamine, threonine, glycine, allo-threonine, serine, O-alkyl serine, aspartic acid, beta-cyanoalanine and valine side chains;

- 5 R<sup>1'</sup> and R<sup>1''</sup> independently represent hydrogen and radicals as defined for R<sup>1</sup>, or one of R<sup>1'</sup> and R<sup>1''</sup>, together with R<sup>1</sup> and the carbon atoms to which R<sup>1</sup>, R<sup>1'</sup> and R<sup>1''</sup> are attached, represent a cycloalkyl radical;
- 10 R<sup>2</sup> represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, -NO<sub>2</sub>, -CN, -CF<sub>3</sub>, -OR<sup>9</sup> and -SR<sup>9</sup>, wherein R<sup>9</sup> represents hydrogen and alkyl radicals;
- 15 R<sup>3</sup> represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and
- 20 disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said
- 25 substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone and sulfoxide derivatives thereof;
- 30 R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen and radicals as defined by R<sup>3</sup> or together with a nitrogen atom to which they are bonded form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and



aryl radicals and the sulfone and sulfoxide derivatives thereof;

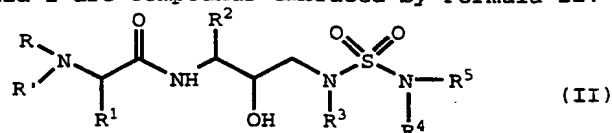
R<sup>6</sup> represents hydrogen and alkyl radicals;

x represents 1 or 2;

t represents either 0, 1 or 2; and

Y represents O, S and NR<sup>15</sup> wherein R<sup>15</sup> represents hydrogen and radicals as defined for R<sup>3</sup>.

A family of compounds of particular interest within Formula I are compounds embraced by Formula II:



wherein:

R represents hydrogen, alkyl, alkenyl, cycloalkyl, hydroxyalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, alkoxycarbonyl, alkoxyalkyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl.

heterocycloalkyl, heterocycloalkyl radicals, or where  
said aminoalkanoyl radical or aminocarbonyl radical is  
disubstituted, said substituents along with the nitrogen  
atom to which they are attached form a heterocycloalkyl  
5 or heteroaryl radical;

R' represents hydrogen and radicals as defined for R<sup>3</sup> or  
R and R' together with the nitrogen to which they are  
attached represent heterocycloalkyl and heteroaryl  
10 radical;

R<sup>1</sup> represents hydrogen, -CH<sub>2</sub>SO<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>, -CO<sub>2</sub>CH<sub>3</sub>,  
-CONH<sub>2</sub>, -CH<sub>2</sub>C(O)NHCH<sub>3</sub>, -C(CH<sub>3</sub>)<sub>2</sub>(SH), -C(CH<sub>3</sub>)<sub>2</sub>(SCH<sub>3</sub>),  
-C(CH<sub>3</sub>)<sub>2</sub>(SC<sub>6</sub>H<sub>5</sub>), -C(CH<sub>3</sub>)<sub>2</sub>(S(O)CH<sub>3</sub>), -C(CH<sub>3</sub>)<sub>2</sub>(S(O)<sub>2</sub>CH<sub>3</sub>),  
15 alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl  
radicals, and amino acid side chains selected from  
asparagine, S-methyl cysteine and methionine and the  
sulfoxide (SO) and sulfone (SO<sub>2</sub>) derivatives thereof,  
isoleucine, allo-isoleucine, alanine, leucine, tert-  
20 leucine, phenylalanine, ornithine, histidine, norleucine,  
glutamine, threonine, glycine, allo-threonine, serine,  
O-methyl serine, aspartic acid, beta-cyanoalanine and  
valine side chains;

25 R<sup>2</sup> represents alkyl, aryl, cycloalkyl, cycloalkylalkyl  
and aralkyl radicals, which radicals are optionally  
substituted with a group selected from alkyl and halogen  
radicals, -NO<sub>2</sub>, -C≡N, CF<sub>3</sub>, -OR<sup>9</sup>, -SR<sup>9</sup>, wherein R<sup>9</sup>  
represents hydrogen and alkyl radicals;

30 R<sup>3</sup> represents alkyl, haloalkyl, alkenyl, alkynyl,  
hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl,  
heterocycloalkyl, heteroaryl, heterocycloalkylalkyl,  
aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and  
35 disubstituted aminoalkyl radicals, wherein said  
substituents are selected from alkyl, aryl, aralkyl,

cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone or sulfoxide derivatives thereof;

10 R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen and radicals as defined by R<sup>3</sup>, or together with the nitrogen atom to which they are bonded represent heterocycloalkyl and heteroaryl radicals.

15 A more preferred family of compounds within Formula II consists of compounds wherein:

R represents hydrogen, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxy carbonyl, aryloxy carbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxy carbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy carbonyl, heteroaroyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals, or where said aminocarbonyl or aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R<sup>3</sup> or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl

5 radical;

R<sup>1</sup> represents CH<sub>2</sub>C(O)NHCH<sub>3</sub>, C(CH<sub>3</sub>)<sub>2</sub>(SCH<sub>3</sub>), C(CH<sub>3</sub>)<sub>2</sub>(S(O)CH<sub>3</sub>), C(CH<sub>3</sub>)<sub>2</sub>(S(O)<sub>2</sub>CH<sub>3</sub>), alkyl, alkenyl and alkynyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, threonine, allo-threonine, isoleucine, tert-leucine, S-methyl cysteine and methionine and the sulfone and sulfoxide derivatives thereof, alanine, and allo-isoleucine;

15

R<sup>2</sup> represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula -OR<sup>9</sup> and -SR<sup>9</sup> wherein R<sup>9</sup> represents alkyl radicals; and

20

R<sup>3</sup> represents alkyl, haloalkyl, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl and heteroaralkyl radicals; and

25

R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkyl and heterocycloalkylalkyl radicals, or R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are bonded from a heterocycloalkyl or heteroaryl radical.

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Of highest interest are compounds within Formula II wherein

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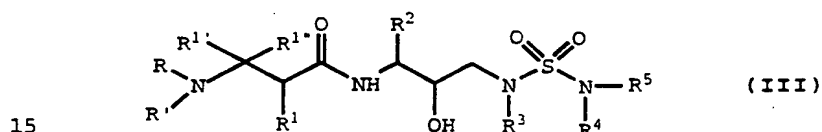
- R represents alkoxy carbonyl, aralkoxy carbonyl, alkyl carbonyl, cycloalkyl carbonyl, cycloalkyl alkoxy carbonyl, cycloalkyl alkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxy carbonyl, aryloxy carbonyl alkyl, 5 aryloxy alkanoyl, heterocyclyl carbonyl, heterocyclyloxy carbonyl, heterocyclyl alkanoyl, heterocyclyl alkoxy carbonyl, heteroaralkanoyl, heteroaralkoxy carbonyl, heteroaryloxy-carbonyl, heteroaroyl, aminocarbonyl, amino alkanoyl, and mono- and 10 disubstituted aminocarbonyl and mono- and disubstituted amino alkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkyl alkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyl radicals, or where 15 said amino alkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;
- 20 R' represents hydrogen and radicals as defined for R<sup>3</sup> or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;
- 25 R<sup>1</sup> represents CH<sub>2</sub>C(O)NHCH<sub>3</sub>, C(CH<sub>3</sub>)<sub>2</sub>(SCH<sub>3</sub>), C(CH<sub>3</sub>)<sub>2</sub>(S[O]CH<sub>3</sub>), C(CH<sub>3</sub>)<sub>2</sub>(S[O]<sub>2</sub>CH<sub>3</sub>), methyl, propargyl, t-butyl, isopropyl and sec-butyl radicals, and amino acid side chains selected from the group consisting of 30 asparagine, valine, S-methyl cysteine, allo-iso-leucine, iso-leucine, and beta-cyano alanine side chains;
- R<sup>2</sup> represents CH<sub>3</sub>SCH<sub>2</sub>CH<sub>2</sub>-, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals;

R<sup>3</sup> represents propyl, isoamyl, n-butyl, isobutyl, cyclohexyl, cyclohexylmethyl, benzyl and pyridylmethyl radicals; and

- 5 R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen and methyl, ethyl, i-propyl, n-butyl, t-butyl, 1,1-dimethylpropyl and phenyl radicals, or together with the nitrogen atom to which they are bonded form a pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl or N'-alkylpiperazinyl radical.

10

Another family of compounds of particular interest within Formula I are compounds embraced by Formula III:



wherein:

- R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxy carbonyl, aryloxy carbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxy carbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals, or where said
- 20
- 25
- 30

aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

- 5 R' represents hydrogen and radicals as defined for R<sup>3</sup> or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;
- 10 R<sup>1</sup> represents hydrogen, -CH<sub>2</sub>SO<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -CH<sub>2</sub>C(O)NHCH<sub>3</sub>, -C(CH<sub>3</sub>)<sub>2</sub>(SH), -C(CH<sub>3</sub>)<sub>2</sub>(SCH<sub>3</sub>), -C(CH<sub>3</sub>)<sub>2</sub>(S(O)CH<sub>3</sub>), -C(CH<sub>3</sub>)<sub>2</sub>(S(O)<sub>2</sub>CH<sub>3</sub>), alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine and methionine and the sulfoxide (SO) and sulfone (SO<sub>2</sub>) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine, allo-threonine, serine, aspartic acid, beta-cyano alanine
- 15 and valine side chains;
- 20

- R<sup>1'</sup> and R<sup>1''</sup> independently represent hydrogen and radicals as defined for R<sup>1</sup>, or one of R<sup>1'</sup> and R<sup>1''</sup>, together with R<sup>1</sup> and the carbon atoms to which R<sup>1</sup>, R<sup>1'</sup> and R<sup>1''</sup> are
- 25 attached, represent a cycloalkyl radical;

- R<sup>2</sup> represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen
- 30 radicals, -NO<sub>2</sub>, -C≡N, CF<sub>3</sub>, -OR<sup>9</sup> and -SR<sup>9</sup>, wherein R<sup>9</sup> represents hydrogen and alkyl radicals;

- R<sup>3</sup> represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and
- 35

disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or  
5 in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone or sulfoxide derivatives  
10 thereof;

R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen and radicals as defined by R<sup>3</sup>, or together with the nitrogen atom to which they are bonded represent heterocycloalkyl and  
15 heteroaryl radicals.

A more preferred family of compounds within Formula III consists of compounds wherein

20 R represents an arylalkanoyl, heteroaroyl, aryloxyalkanoyl, aryloxycarbonyl, alkanoyl, aminocarbonyl, mono-substituted aminoalkanoyl, or disubstituted aminoalkanoyl, or mono-or dialkylaminocarbonyl radical;

25 R' represents hydrogen and radicals as defined for R<sup>3</sup> or R and R' together with the nitrogen to which they are attached represent a heterocycloalkyl or heteroaryl radical;

30 R<sup>1</sup>, R<sup>1'</sup> and R<sup>1''</sup> independently represent hydrogen and alkyl radicals having from 1 to about 4 carbon atoms, alkenyl, alkynyl, aralkyl radicals, and radicals represented by the formula -CH<sub>2</sub>C(O)R" or -C(O)R" wherein  
35 R" represents R<sup>38</sup>, -NR<sup>38</sup>R<sup>39</sup> and OR<sup>38</sup> wherein R<sup>38</sup> and R<sup>39</sup>



independently represent hydrogen and alkyl radicals having from 1 to about 4 carbon atoms;

- 5  $R^2$  represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula  $-OR^9$  and  $-SR^9$  wherein  $R^9$  represents hydrogen and alkyl radicals; and
- 10  $R^3$  represents alkyl, haloalkyl, alkenyl, alkynyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl radicals; and
- 15  $R^4$  and  $R^5$  independently represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkyl and heterocycloalkylalkyl radicals, or  $R^4$  and  $R^5$  together with the nitrogen atom to which they are bonded form a heterocycloalkyl or
- 20 heteroaryl radical.

Of highest interest are compounds of Formula III wherein:

- 25  $R$  represents an arylalkanoyl, aryloxycarbonyl, aryloxyalkanoyl, alkanoyl, aminocarbonyl, mono-substituted aminoalkanoyl, or disubstituted aminoalkanoyl, or mono-or dialkylaminocarbonyl radical;
- 30  $R'$  represents hydrogen and radicals as defined for  $R^3$  or  $R$  and  $R'$  together with the nitrogen to which they are attached represent a heterocycloalkyl or heteroaryl radical;

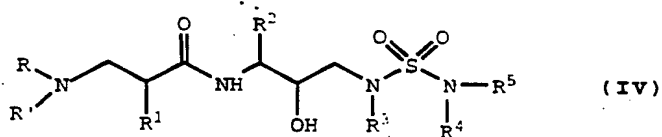
R<sup>1</sup>, R<sup>1'</sup> and R<sup>1''</sup> independently represent hydrogen, methyl, ethyl, benzyl, phenylpropyl, -C(O)NH<sub>2</sub> and propargyl radicals;

5 R<sup>2</sup> represents CH<sub>3</sub>SCH<sub>2</sub>CH<sub>2</sub>-, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals;

10 R<sup>3</sup> represents propyl, isobutyl, isoamyl, n-butyl, cyclohexyl, cyclohexylmethyl, benzyl and pyridylmethyl radicals; and

15 R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen and methyl, ethyl, i-propyl, n-butyl, t-butyl, 1,1-dimethylpropyl, cyclohexyl and phenyl radicals, or together with the nitrogen atom to which they are bonded form a pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl radical.

20 Another family of compounds of particular interest within Formula I are compounds embraced by Formula IV:



25

wherein:

30 R represents hydrogen, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl,

- heterocyclylcarbonyl, heterocyclyloxy carbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy carbonyl, heteroaroyl, aminocarbonyl, aminoalkanoyl, and
- 5 mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals, or where
- 10 said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;
- 15 R' represents hydrogen and radicals as defined for R<sup>3</sup> or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;
- 20 R<sup>1</sup> represents hydrogen, -CH<sub>2</sub>SO<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -CH<sub>2</sub>C(O)NHCH<sub>3</sub>, -C(CH<sub>3</sub>)<sub>2</sub>(SH), -C(CH<sub>3</sub>)<sub>2</sub>(SCH<sub>3</sub>), -C(CH<sub>3</sub>)<sub>2</sub>(SC<sub>6</sub>H<sub>5</sub>), -C(CH<sub>3</sub>)<sub>2</sub>(S(O)CH<sub>3</sub>), -C(CH<sub>3</sub>)<sub>2</sub>(S(O)<sub>2</sub>CH<sub>3</sub>), alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from
- 25 asparagine, S-methyl cysteine and methionine and the sulfoxide (SO) and sulfone (SO<sub>2</sub>) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine, allo-threonine, serine,
- 30 aspartic acid, beta-cyano alanine and valine side chains;
- R<sup>2</sup> represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally
- 35 substituted with a group selected from alkyl and halogen

radicals,  $-\text{NO}_2$ ,  $-\text{C}\equiv\text{N}$ ,  $\text{CF}_3$ ,  $-\text{OR}^9$ ,  $-\text{SR}^9$ , wherein  $\text{R}^9$  represents hydrogen and alkyl;

$\text{R}^3$  represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone or sulfoxide derivatives thereof;

$\text{R}^4$  and  $\text{R}^5$  independently represent hydrogen and radicals as defined for  $\text{R}^3$  or together with a nitrogen atom to which they are bonded form a heterocycloalkyl or a heteroaryl radical.

A more preferred family of compounds within Formula IV consists of compounds wherein

$\text{R}$  represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxy carbonyl, aryloxy carbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxy carbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl,

aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R<sup>3</sup> or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

R<sup>1</sup> represents hydrogen, alkyl and alkenyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, threonine, allo-threonine, isoleucine, tert-leucine, S-methyl cysteine and the sulfone and sulfoxide derivatives thereof, alanine, and allo-isoleucine;

R<sup>2</sup> represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula -OR<sup>9</sup> and -SR<sup>9</sup> wherein R<sup>9</sup> represents hydrogen and alkyl and halogen radicals;

R<sup>3</sup> represents alkyl, halalkyl, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl radicals; and

R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl,

heteroaralkyl, heterocycloalkyl and heterocycloalkylalkyl radicals, or R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are bonded from a heterocycloalkyl or heteroaryl radical.

5

Of highest interest are compounds within Formula IV wherein

10 R represents hydrogen, alkoxy carbonyl, aralkoxy carbonyl, alkyl carbonyl, cycloalkyl carbonyl, cycloalkylalkoxy carbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxy carbonyl, aryloxy carbonylalkyl, aryloxyalkanoyl, heterocyclyl carbonyl, heterocyclyloxy carbonyl, heterocyclylalkanoyl, 15 heterocyclylalkoxy carbonyl, heteroaralkanoyl, heteroaralkoxy carbonyl, heteroaryloxy-carbonyl, heteroaroyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are 20 selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they 25 are attached form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R<sup>3</sup> or R and R' together with the nitrogen to which they are 30 attached represent heterocycloalkyl and heteroaryl radical;

R<sup>1</sup> represents hydrogen, methyl, propargyl, t-butyl, isopropyl and sec-butyl radicals, and amino acid side 35 chains selected from the group consisting of asparagine, valine, S-methyl cysteine, allo-iso-leucine, iso-leucine,

threonine, serine, aspartic acid, beta-cyano alanine, and  
allo-threonine side chains;

R<sup>2</sup> represents CH<sub>3</sub>SCH<sub>2</sub>CH<sub>2</sub>-, iso-butyl, n-butyl, benzyl,  
5 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl  
radicals;

R<sup>3</sup> represents propyl, isobutyl, isoamyl, n-butyl,  
cyclohexyl, cyclohexylmethyl, benzyl and pyridylmethyl  
10 radicals; and

R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen and methyl,  
ethyl, i-propyl, n-butyl, t-butyl, 1,1-dimethylpropyl,  
cyclohexyl and phenyl radicals, or R<sup>4</sup> and R<sup>5</sup> together  
15 with the nitrogen atom to which they are bonded form a  
pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl  
radical.

As utilized herein, the term "alkyl", alone or  
20 in combination, means a straight-chain or branched-chain  
alkyl radical containing from 1 to about 10, preferably  
from 1 to 8, carbon atoms. Examples of such radicals  
include methyl, ethyl, n-propyl, isopropyl, n-butyl,  
isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl,  
25 octyl and the like. The term "alkenyl", alone or in  
combination, means a straight-chain or branched-chain  
hydrocarbon radical having one or more double bonds and  
containing from 2 to about 18 carbon atoms preferably  
from 2 to 8 carbon atoms. Examples of suitable alkenyl  
30 radicals include ethenyl, propenyl, 1,4-butadienyl,  
12-octadecene and the like. The term "alkynyl", alone or  
in combination, means a straight-chain hydrocarbon  
radical having one or more triple bonds and containing  
from 2 to about 10 carbon atoms, preferably from 2 to 8  
35 carbon atoms. Examples of alkynyl radicals include  
ethynyl, propynyl, (propargyl), butynyl and the like.

The term "alkoxy", alone or in combination, means an alkyl ether radical wherein the term alkyl is as defined above. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like. The term "cycloalkyl", alone or in combination, means a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety contains from about 3 to about 8 carbon atoms and is cyclic. The term "cycloalkylalkyl" means an alkyl radical as defined above which is substituted by a cycloalkyl radical containing from about 3 to about 8, preferably from 3 to 6 carbon atoms. Examples of such cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. The term "aryl", alone or in combination, means a phenyl or naphthyl radical which optionally carries one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl, 2-naphthyl, and the like. The term "aralkyl", alone or in combination, means an alkyl radical as defined above in which one hydrogen atom is replaced by an aryl radical as defined above, such as benzyl, 2-phenylethyl and the like. The term "aralkoxy carbonyl", alone or in combination, means a radical of the formula  $-C(O)-O-aralkyl$  in which the term "aralkyl" has the significance given above. An example of an aralkoxycarbonyl radical is benzyloxycarbonyl. The term "aryloxy" means a radical of the formula  $aryl-O-$  in which the term aryl has the significance given above. The term "alkanoyl", alone or in combination, means an acyl radical derived from an alkanecarboxylic acid wherein alkane means a radical as defined above for alkyl. Examples of alkanoyl radicals include acetyl, propionyl,



butyryl, valeryl, 4-methylvaleryl, and the like. The term "cycloalkylcarbonyl" means an acyl group derived from a monocyclic or bridged cycloalkanecarboxylic acid such as cyclopropanecarbonyl, cyclohexanecarbonyl, 5 adamantanecarbonyl, and the like, or from a benz-fused monocyclic cycloalkanecarboxylic acid which is optionally substituted by, for example, alkanoylamino, such as 1,2,3,4-tetrahydro-2-naphthoyl, 2-acetamido-1,2,3,4-tetrahydro-2-naphthoyl. The term "aralkanoyl" means an 10 acyl radical derived from an aryl-substituted alkanecarboxylic acid such as phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminohydrocinnamoyl, 4-methoxyhydrocinnamoyl, and the 15 like. The term "aroyl" means an acyl radical derived from an aromatic carboxylic acid. Examples of such radicals include aromatic carboxylic acids, an optionally substituted benzoic or naphthoic acid such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 20 4-(benzyloxycarbonyl)benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-2 naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamido)-2-naphthoyl, and the like. The heterocyclyl or heterocycloalkyl portion of a 25 heterocyclylcarbonyl, heterocycliloxycarbonyl, heterocyclylalkoxycarbonyl, or heterocyclialkyl group or the like is a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle which contains one or more hetero atoms selected from nitrogen, 30 oxygen and sulphur, which is optionally substituted on one or more carbon atoms by halogen, alkyl, alkoxy, oxo, and the like, and/or on a secondary nitrogen atom (i.e., -NH-) by alkyl, aralkoxycarbonyl, alkanoyl, phenyl or phenylalkyl or on a tertiary nitrogen atom (i.e. = N-) by 35 oxido and which is attached via a carbon atom. The heteroaryl portion of a heteroaroyl,

heteroaryloxycarbonyl, or a heteroalkoxy carbonyl group or the like is an aromatic monocyclic, bicyclic, or tricyclic heterocycle which contains the hetero atoms and is optionally substituted as defined above with respect to the definition of heterocyclyl. Such heterocyclyl and heteroaryl radicals have from four to about 12 ring members, preferably from 4 to 10 ring members. Examples of such heterocyclyl and heteroaryl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, pyrrolyl, imidazolyl (e.g., imidazol-4-yl, 1-benzylloxycarbonylimidazol-4-yl, etc.), pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, furyl, thienyl, triazolyl, oxazolyl, thiazolyl, indolyl (e.g., 2-indolyl, etc.), quinolinyl, (e.g., 2-quinolinyl, 3-quinolinyl, 1-oxido-2-quinolinyl, etc.), isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, etc.), tetrahydroquinolinyl (e.g., 1,2,3,4-tetrahydro-2-quinolyl, etc.), 1,2,3,4-tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydro-1-oxo-isoquinolinyl, etc.), quinoxalinyl, 8-carbolinyl, 2-benzofuran-carbonyl, 1-,2-,4- or 5-benzimidazolyl, and the like. The term "cycloalkylalkoxycarbonyl" means an acyl group derived from a cycloalkylalkoxycarboxylic acid of the formula cycloalkylalkyl-O-COOH wherein cycloalkylalkyl has the significance given above. The term "aryloxyalkanoyl" means an acyl radical of the formula aryl-O-alkanoyl wherein aryl and alkanoyl have the significance given above. The term "heterocyclylloxycarbonyl" means an acyl group derived from heterocyclyl-O-COOH wherein heterocyclyl is as defined above. The term "heterocyclylalkanoyl" is an acyl radical derived from a heterocyclyl-substituted alkane carboxylic acid wherein heterocyclyl has the significance given above. The term "heterocyclylalkoxycarbonyl" means an acyl radical derived from a heterocyclyl-substituted alkane-O-COOH wherein heterocyclyl has the significance given above.

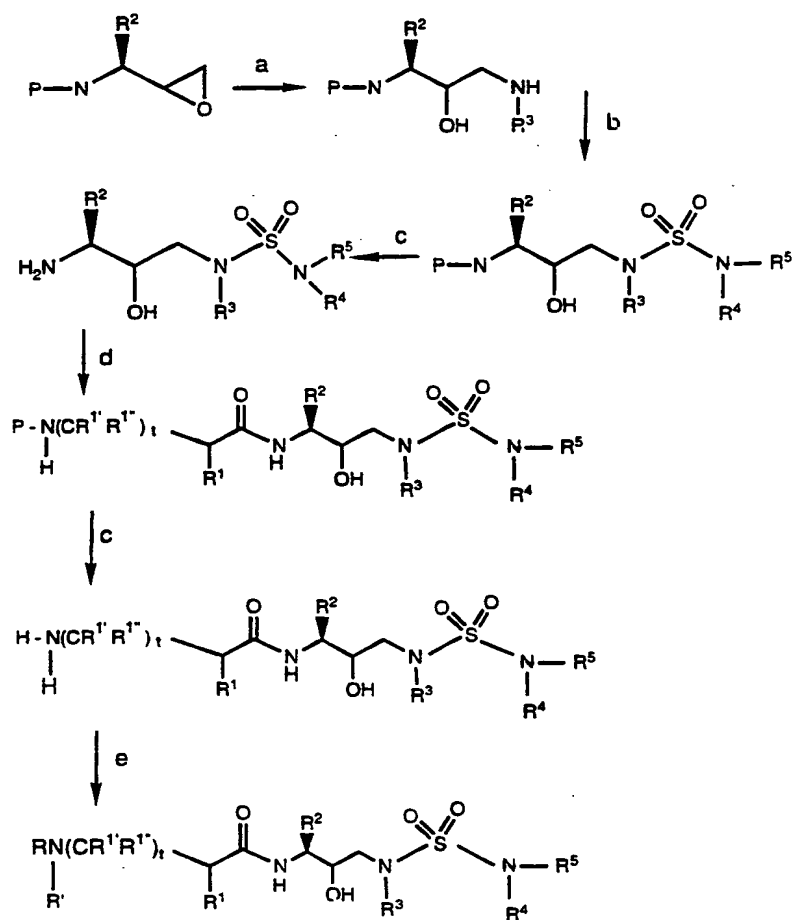
The term "heteroaryloxy carbonyl" means an acyl radical derived from a carboxylic acid represented by heteroaryl-O-COOH wherein heteroaryl has the significance given above. The term "aminocarbonyl" alone or in combination, means an amino-substituted carbonyl (carbamoyl) group derived from an amino-substituted carboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from hydrogen, and alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like. The term "aminoalkanoyl" means an acyl group derived from an amino-substituted alkanecarboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from hydrogen, and alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like. The term "halogen" means fluorine, chlorine, bromine or iodine. The term "haloalkyl" means an alkyl radical having the significance as defined above wherein one or more hydrogens are replaced with a halogen. Examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like. The term "leaving group" generally refers to groups readily displaceable by a nucleophile, such as an amine, a thiol or an alcohol nucleophile. Such leaving groups are well known in the art. Examples of such leaving groups include, but are not limited to, N-hydroxysuccinimide, N-hydroxybenzotriazole, halides, triflates, tosylates and the like. Preferred leaving groups are indicated herein where appropriate.

Procedures for preparing the compounds of Formula I are set forth below. It should be noted that the general procedure is shown as it relates to preparation of compounds having the specified

stereochemistry, for example, wherein the absolute stereochemistry about the hydroxyl group is designated as (R), which is the preferred stereochemistry for the compounds of the present invention. However, such  
5 procedures are generally applicable to those compounds of opposite configuration, e.g., where the stereochemistry about the hydroxyl group is (S). In addition, the compounds having the (R) stereochemistry can be utilized to produce those having the (S) stereochemistry. For  
10 example, a compound having the (R) stereochemistry can be inverted to the (S) stereochemistry using well-known methods.

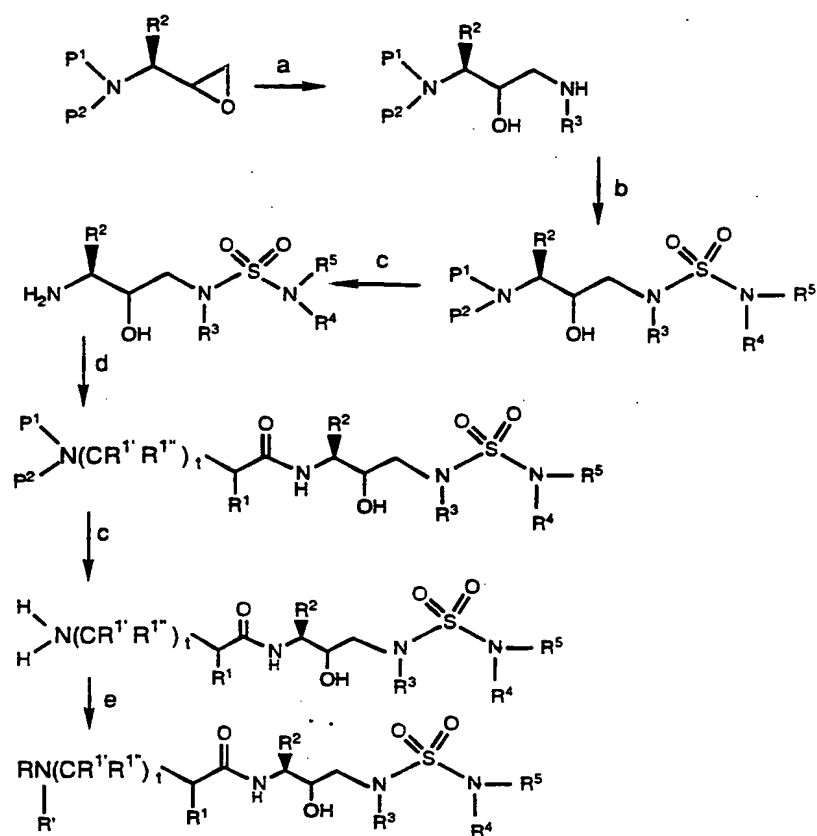
15                   Preparation of Compounds of Formula I

The compounds of the present invention represented by Formula I above can be prepared utilizing the following general procedure. This procedure is  
20 schematically shown in the following Schemes I and II:

SCHEME I

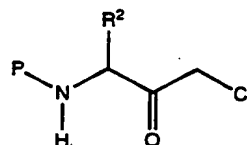
a) amine b) sulfamoyl chloride  $R^4R^5NSO_2Cl$  (or anhydride)  
 + acid scavenger c) deprotection d) coupling  
 e) coupling.

## SCHEME II



a) amine b) sulfamoyl chloride  $R^4R^5NSO_2Cl$  (or anhydride)  
 + acid scavenger c) deprotection d) coupling  
 e) coupling.

An N-protected chloroketone derivative of an amino acid having the formula:

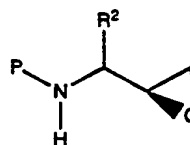


5 wherein P represents an amino protecting group, and R<sup>2</sup> is as defined above, is reduced to the corresponding alcohol utilizing an appropriate reducing agent. Suitable amino protecting groups are well known in the art and include carbobenzoxy, t-butoxycarbonyl, and the like. A preferred amino protecting group is carbobenzoxy. A preferred N-protected chloroketone is N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone. A preferred reducing agent is sodium borohydride. The reduction reaction is conducted at a temperature of from -10°C to about 25°C, preferably at about 0°C, in a suitable solvent system such as, for example, tetrahydrofuran, and the like. The N-protected chloroketones are commercially available, e.g., such as from Bachem, Inc., Torrance, California. Alternatively, the chloroketones can be prepared by the procedure set forth in S. J. Fittkau, J. Prakt. Chem., 315, 1037 (1973), and subsequently N-protected utilizing procedures which are well known in the art.

25 The halo alcohol can be utilized directly, as described below, or, preferably, is then reacted, preferably at room temperature, with a suitable base in a suitable solvent system to produce an N-protected amino epoxide of the formula:

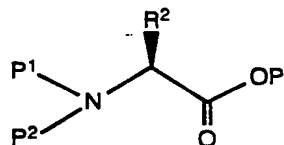
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29



wherein P and R<sup>2</sup> are as defined above. Suitable solvent systems for preparing the amino epoxide include ethanol, methanol, isopropanol, tetrahydrofuran, dioxane, and the like including mixtures thereof. Suitable bases for producing the epoxide from the reduced chloroketone include potassium hydroxide, sodium hydroxide, potassium t-butoxide, DBU and the like. A preferred base is potassium hydroxide.

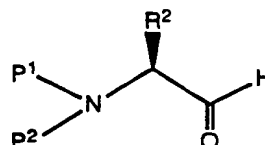
Alternatively, a protected amino epoxide can be prepared starting with an L-amino acid which is reacted with a suitable amino-protecting group in a suitable solvent to produce an amino-protected L-amino acid ester of the formula:



wherein P<sup>1</sup> and P<sup>2</sup> independently represent hydrogen, benzyl and amino-protecting groups (as defined above), provided that P<sup>1</sup> and P<sup>2</sup> are not both hydrogen; P<sup>3</sup> represents carboxyl-protecting group, e.g., methyl, ethyl, benzyl, tertiary-butyl and the like; and R<sup>2</sup> is as defined above.



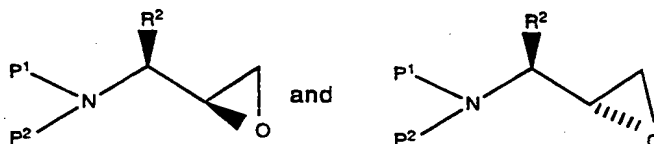
The amino-protected L-amino acid ester is then reduced, to the corresponding alcohol. For example, the amino-protected L-amino acid ester can be reduced with diisobutylaluminum hydride at  $-78^{\circ}\text{C}$  in a suitable solvent such as toluene. The resulting alcohol is then converted, for example, by way of a Swern oxidation, to the corresponding aldehyde of the formula:



10

wherein  $P^1$ ,  $P^2$  and  $R^2$  are as defined above. Thus, a dichloromethane solution of the alcohol is added to a cooled ( $-75$  to  $-68^{\circ}\text{C}$ ) solution of oxalyl chloride in dichloromethane and DMSO in dichloromethane and stirred for 35 minutes.

The aldehyde resulting from the Swern oxidation is then reacted with a halomethyl lithium reagent, which reagent is generated *in situ* by reacting an alkyl lithium or aryllithium compound with a dihalomethane represented by the formula  $X^1\text{CH}_2\text{X}^2$  wherein  $X^1$  and  $X^2$  independently represent I, Br or Cl. For example, a solution of the aldehyde and chloriodomethane in THF is cooled to  $-78^{\circ}\text{C}$  and a solution of n-butyllithium in hexane is added. The resulting product is a mixture of diastereomers of the corresponding amino-protected epoxides of the formulas:

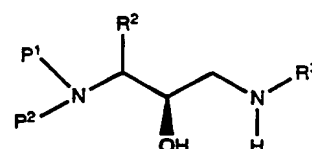
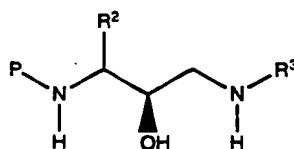


The diastereomers can be separated e.g., by chromatography, or, alternatively, once reacted in subsequent steps the diastereomeric products can be separated. For compounds having the (S) stereochemistry, a D-amino acid can be utilized in place of the L-amino acid.

The amino epoxide is then reacted, in a suitable solvent system, with an equal amount, or preferably an excess of, a desired amine of the formula:

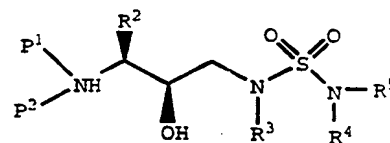
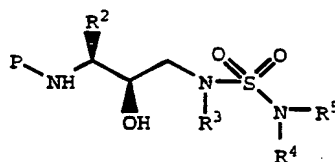


wherein  $R^3$  is hydrogen or is as defined above. The reaction can be conducted over a wide range of temperatures, e.g., from about 10°C to about 100°C, but is preferably, but not necessarily, conducted at a temperature at which the solvent begins to reflux. Suitable solvent systems include protic, non-protic and dipolar aprotic organic solvents such as, for example, those wherein the solvent is an alcohol, such as methanol, ethanol, isopropanol, and the like, ethers such as tetrahydrofuran, dioxane and the like, and toluene, N,N-dimethylformamide, dimethyl sulfoxide, and mixtures thereof. A preferred solvent is isopropanol. Exemplary amines corresponding to the formula  $R^3NH_2$  include benzyl amine, isobutylamine, n-butyl amine, isopentyl amine, isoamylamine, cyclohexanemethyl amine, naphthylene methyl amine and the like. The resulting product is a 3-(N-protected amino)-3-( $R^2$ )-1-(NHR<sup>3</sup>)-propan-2-ol derivative (hereinafter referred to as an amino alcohol) can be represented by the formulas:



wherein P, P<sup>1</sup>, P<sup>2</sup>, R<sup>2</sup> and R<sup>3</sup> are as described above.  
 Alternatively, a haloalcohol can be utilized in place of  
 5 the amino epoxide.

The amino alcohol defined above is then reacted  
 in a suitable solvent with a sulfamoyl halide, e.g.  
 sulfamoyl chloride (R<sup>4</sup>R<sup>5</sup>NSO<sub>2</sub>Cl or R<sup>4</sup>HNSO<sub>2</sub>Cl) or sulfamoyl  
 10 anhydride in the presence of an acid scavenger. Suitable  
 solvents in which the reaction can be conducted include  
 methylene chloride, tetrahydrofuran. Suitable acid  
 scavengers include triethylamine, pyridine. The resulting  
 sulfamic acid derivative can be represented, depending on  
 15 the epoxide utilized, by the formulas;



wherein P, P<sup>1</sup>, P<sup>2</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined above.  
 20 These intermediates are useful for preparing inhibitor  
 compounds of the present invention and are also active  
 inhibitors of retroviral proteases.

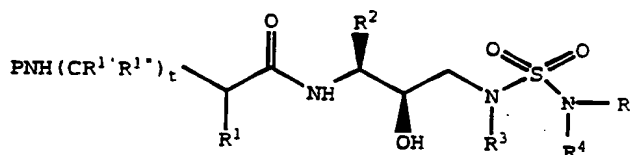
The sulfamoyl halides of the formula R<sup>4</sup>NHSO<sub>2</sub>X  
 25 can be prepared by the reaction of a suitable isocyanate  
 of the formula R<sup>4</sup>NCO with fuming sulfuric acid to produce  
 the corresponding sulfamate which is then converted to the  
 halide by well known procedures, such as by treating the

sulfamate with  $\text{PCl}_5$ . Alternatively the isocyanate can be treated with chlorosulfonic acid to produce the corresponding sulfamoyl chloride directly.

5           The sulfamoyl halides of the formula  $\text{R}^4\text{R}^5\text{NSO}_2\text{Cl}$  can be prepared by reacting an amine of the formula  $\text{R}^4\text{R}^5\text{NH}$ , preferably as a salt such as the hydrochloride, with sulfonyl chloride in a suitable solvent such as acetonitrile. The reaction mixture is gradually warmed to  
10 reflux temperature and maintained at the reflux temperature until the reaction is complete. Alternatively, sulfamoyl halides of the formula  $\text{R}^4\text{R}^5\text{NSO}_2\text{Cl}$  can be prepared by reacting an amine of the formula  $\text{R}^4\text{R}^5\text{NH}$  with sulfonyl chloride in boiling MeCN as disclosed in  
15 Matier et al., J. Med. Chem., 15, No. 5, p.538 (1972).

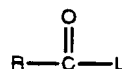
Following preparation of the sulfamic acid derivative, the amino protecting group P or  $\text{P}^1$  and  $\text{P}^2$  amino protecting groups are removed under conditions which  
20 will not affect the remaining portion of the molecule. These methods are well known in the art and include acid hydrolysis, hydrogenolysis and the like. A preferred method involves removal of the protecting group, e.g., removal of a carbobenzoxy group, by hydrogenolysis  
25 utilizing palladium on carbon in a suitable solvent system such as an alcohol, acetic acid, and the like or mixtures thereof. Where the protecting group is a t-butoxycarbonyl group, it can be removed utilizing an inorganic or organic acid, e.g., HCl or trifluoroacetic acid, in a suitable  
30 solvent system, e.g., dioxane or methylene chloride. The resulting product is the amine salt derivative. Following neutralization of the salt, the amine is then reacted with an amino acid or corresponding derivative thereof represented by the formula  $(\text{PN}[\text{CR}^1 \text{ R}^2])_t \text{CH}(\text{R}^3)\text{COOH}$   
35 wherein t,  $\text{R}^1$ ,  $\text{R}^2$  and  $\text{R}^3$  are as defined above, to

produce the antiviral compounds of the present invention having the formula:



5 wherein t, P, R¹, R¹', R¹'', R², R³, R⁴ and R⁵ are as defined above. Preferred protecting groups in this instance are a benzyloxycarbonyl group or a t-butoxycarbonyl group. Where the amine is reacted with a  
 10 derivative of an amino acid, e.g., when t=1 and R¹' and R¹'' are both H, so that the amino acid is a β-amino acid, such β-amino acids can be prepared according to the procedure set forth in a copending application, U. S.  
 15 Serial No. 07/345,808. Where t is 1, one of R¹' and R¹'' is H and R¹ is hydrogen so that the amino acid is a homo-β-amino acid, such homo-β-amino acids can be prepared by the procedure set forth in a copending application, U.S.  
 20 Serial No. 07/853,561. Where t is 0 and R¹ is alkyl, alkenyl, alkynyl, cycloalkyl, -CH₂SO₂NH₂, -CH₂CO₂CH₃, -CO₂CH₃, -CONH₂, -CH₂C(O)NHCH₃, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), -C(CH₃)₂[S(O)CH₃], -C(CH₃)₂[S(O₂)CH₃], or an amino acid side chain, such materials are well known and many are commercially available from Sigma-Aldrich.

25 The N-protecting group can be subsequently removed, if desired, utilizing the procedures described above, and then reacted with a carboxylate represented by the formula:



30

wherein R is as defined above and L is an appropriate leaving group such as a halide. Preferably, where R<sup>1</sup> is a side chain of a naturally occurring  $\alpha$ -amino acid, R is a 2-quinoline carbonyl group derived from

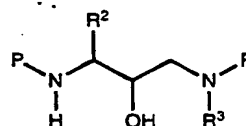
5 N-hydroxysuccinimide-2-quinoline carboxylate, i.e., L is hydroxy succinimide. A solution of the free amine (or amine acetate salt) and about 1.0 equivalent of the carboxylate are mixed in an appropriate solvent system and optionally treated with up to five equivalents of a base

10 such as, for example, N-methylmorpholine, at about room temperature. Appropriate solvent systems include tetrahydrofuran, methylene chloride or N,N-dimethylformamide, and the like, including mixtures thereof.

15

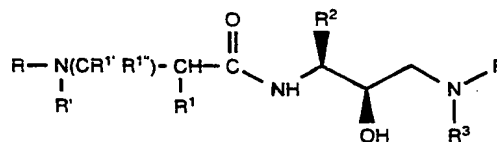
Alternatively, the protected amino alcohol from the epoxide opening can be further protected at the newly introduced amino group with a protecting group P' which is not removed when the first protecting P is removed. One

20 skilled in the art can choose appropriate combinations of P and P'. One suitable choice is when P is Cbz and P' is Boc. The resulting compound represented by the formula:



25

can be carried through the remainder of the synthesis to provide a compound of the formula:



30

and the new protecting group P' is selectively removed, and following deprotection, the resulting amine reacted to form the sulfamic acid derivative as described above. This selective deprotection and conversion to the sulfamic acid can be accomplished at either the end of the synthesis or at any appropriate intermediate step if desired.

It is contemplated that for preparing compounds of the Formulas having R<sup>6</sup>, the compounds can be prepared following the procedure set forth above and, prior to coupling the sulfonamide derivative or analog thereof, e.g. coupling to the amino acid PNH(CH<sub>2</sub>)<sub>t</sub>CH(R<sup>1</sup>)COOH, carried through a procedure referred to in the art as reductive amination. Thus, a sodium cyanoborohydride and an appropriate aldehyde or ketone can be reacted with the sulfonamide derivative compound or appropriate analog at room temperature in order to reductively aminate any of the compounds of Formulas I-IV. It is also contemplated that where R<sup>3</sup> of the amino alcohol intermediate is hydrogen, the inhibitor compounds of the present invention wherein R<sup>3</sup> is alkyl, or other substituents wherein the α-C contains at least one hydrogen, can be prepared through reductive amination of the final product of the reaction between the amino alcohol and the amine or at any other stage of the synthesis for preparing the inhibitor compounds.

Contemplated equivalents of the general formulas set forth above for the antiviral compounds and derivatives as well as the intermediates are compounds otherwise corresponding thereto and having the same general properties, such as tautomers thereof as well as compounds, wherein one or more of the various R groups are simple variations of the substituents as defined therein, e.g., wherein R is a higher alkyl group than that

indicated. In addition, where a substituent is designated as, or can be, a hydrogen, the exact chemical nature of a substituent which is other than hydrogen at that position, e.g., a hydrocarbyl radical or a halogen, hydroxy, amino and the like functional group, is not critical so long as it does not adversely affect the overall activity and/or synthesis procedure.

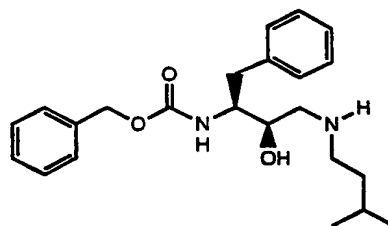
The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily preparable from known starting materials.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.



The following Examples 1 through 9 illustrate preparation of intermediates. These intermediates are useful in preparing the inhibitor compounds of the present invention as illustrated in Examples 13-17. In addition, the intermediates of Examples 4-9 are also retroviral protease inhibitors and inhibit, in particular, HIV protease.

Example 1



Preparation of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]-N-isoamylamine

Part A:

To a solution of 75.0g (0.226 mol) of N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone in a mixture of 807 mL of methanol and 807 mL of tetrahydrofuran at -2°C, was added 13.17g (0.348 mol, 1.54 equiv.) of solid sodium borohydride over one hundred minutes. The solvents were removed under reduced pressure at 40°C and the residue dissolved in ethyl acetate (approx. 1L). The solution was washed sequentially with 1M potassium hydrogen sulfate, saturated sodium bicarbonate and then saturated sodium chloride solutions. After drying over anhydrous magnesium sulfate and filtering, the solution was removed under reduced pressure. To the resulting oil was added hexane (approx. 1L) and the mixture warmed to 60°C with

swirling. After cooling to room temperature, the solids were collected and washed with 2L of hexane. The resulting solid was recrystallized from hot ethyl acetate and hexane to afford 32.3g (43% yield) of

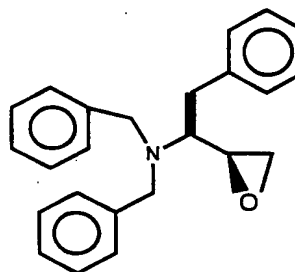
- 5 N-benzyloxycarbonyl-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol, mp 150-151°C and  $M+Li^+ = 340$ .

Part B:

- To a solution of 6.52g (0.116 mol, 1.2 equiv.)  
10 of potassium hydroxide in 968 mL of absolute ethanol at room temperature, was added 32.3g (0.097 mol) of N-CBZ-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol. After stirring for fifteen minutes, the solvent was removed under reduced pressure and the solids dissolved in  
15 methylene chloride. After washing with water, drying over magnesium sulfate, filtering and stripping, one obtains 27.9g of a white solid. Recrystallization from hot ethyl acetate and hexane afforded 22.3g (77% yield) of N-benzyloxycarbonyl-3(S)-amino-1,2(S)-epoxy-4-  
20 phenylbutane, mp 102-103°C and  $MH^+ 298$ .

Part C:

- A solution of N-benzyloxycarbonyl 3(S)-amino-1,2-(S)-epoxy-4-phenylbutane (1.00g, 3.36 mmol) and  
25 isoamylamine (4.90g, 67.2 mmol, 20 equiv.) in 10 mL of isopropyl alcohol was heated to reflux for 1.5 hours. The solution was cooled to room temperature, concentrated in vacuo and then poured into 100 mL of stirring hexane whereupon the product crystallized from solution. The  
30 product was isolated by filtration and air dried to give 1.18g, 95% of N-[[3(S)-phenylmethylcarbamoyl]amino-2(R)-hydroxy-4-phenylbutyl]N-[(3-methylbutyl)]amine mp 108.0-109.5°C,  $MH^+ m/z = 371$ .

Example 2

5 Preparation of N,N-dibenzyl-3(S)-amino-1,2-(S)-epoxy-4-  
phenylbutane

Step A:

10 A solution of L-phenylalanine (50.0 g, 0.302 mol), sodium hydroxide (24.2 g, 0.605 mol) and potassium carbonate (83.6 g, 0.605 mol) in water (500 ml) is heated to 97°C. Benzyl bromide (108.5 ml, 0.912 mol) is then slowly added (addition time ~25 min). The mixture is then stirred at 97°C for 30 minutes. The solution is  
15 cooled to room temperature and extracted with toluene (2 x 250 ml). The combined organic layers are then washed with water, brine, dried over magnesium sulfate, filtered and concentrated to give an oil product. The crude product is then used in the next step without  
20 purification.

Step B:

The crude benzylated product of the above step is dissolved in toluene (750 ml) and cooled to -55°C. A  
25 1.5 M solution of DIBAL-H in toluene (443.9 ml, 0.666 mol) is then added at a rate to maintain the temperature between -55° to -50°C (addition time - 1 hour). The

- mixture is stirred for 20 minutes at -55°C. The reaction is quenched at -55°C by the slow addition of methanol (37 ml). The cold solution is then poured into cold (5°C) 1.5 N HCl solution (1.8 L). The precipitated solid
- 5 (approx. 138 g) is filtered off and washed with toluene. The solid material is suspended in a mixture of toluene (400 ml) and water (100 ml). The mixture is cooled to 5°C, treated with 2.5 N NaOH (186 ml) and then stirred at room temperature until the solid is dissolved. The
- 10 toluene layer is separated from the aqueous phase and washed with water and brine, dried over magnesium sulfate, filtered and concentrated to a volume of 75 ml (89 g). Ethyl acetate (25 ml) and hexane (25 ml) are then added to the residue upon which the alcohol product
- 15 begins to crystallize. After 30 min., an additional 50 ml hexane is added to promote further crystallization. The solid is filtered off and washed with 50 ml hexane to give approximately 35 g of material. A second crop of material can be isolated by refiltering the mother liquor.
- 20 The solids are combined and recrystallized from ethyl acetate (20 ml) and hexane (30 ml) to give, in 2 crops, approximately 40 g (40% from L-phenylalanine) of analytically pure alcohol product. The mother liquors are combined and concentrated (34 g). The residue is
- 25 treated with ethyl acetate and hexane which provides an additional 7 g (~7% yield) of slightly impure solid product. Further optimization in the recovery from the mother liquor is probable.
- 30 Step C:
- A solution of oxalyl chloride (8.4 ml, 0.096 mol) in dichloromethane (240 ml) is cooled to -74°C. A solution of DMSO (12.0 ml, 0.155 mol) in dichloromethane (50 ml) is then slowly added at a rate to maintain the
- 35 temperature at -74°C (addition time ~1.25 hr). The

mixture is stirred for 5 min. followed by addition of a solution of the alcohol (0.074 mol) in 100 ml of dichloromethane (addition time -20 min., temp. -75°C to -68°C). The solution is stirred at -78°C for 35 minutes.

5 Triethylamine (41.2 ml, 0.295 mol) is then added over 10 min. (temp. -78° to -68°C) upon which the ammonium salt precipitated. The cold mixture is stirred for 30 min. and then water (225 ml) is added. The dichloromethane layer is separated from the aqueous phase and washed with

10 water, brine, dried over magnesium sulfate, filtered and concentrated. The residue is diluted with ethyl acetate and hexane and then filtered to further remove the ammonium salt. The filtrate is concentrated to give the desired aldehyde product. The aldehyde was carried on to

15 the next step without purification.

Temperatures higher than -70°C have been reported in the literature for the Swern oxidation. Other Swern modifications and alternatives to the Swern

20 oxidations are also possible.

A solution of the crude aldehyde 0.074 mol and chloriodomethane (7.0 ml, 0.096 mol) in tetrahydrofuran (285 ml) is cooled to -78°C. A 1.6 M solution of

25 n-butyllithium in hexane (25 ml, 0.040 mol) is then added at a rate to maintain the temperature at -75°C (addition time - 15 min.). After the first addition, additional chloriodomethane (1.6 ml, 0.022 mol) is added again, followed by n-butyllithium (23 ml, 0.037 mol), keeping

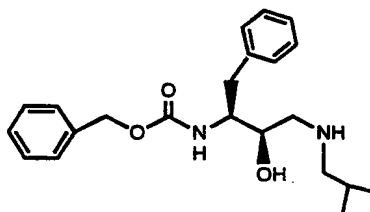
30 the temperature at -75°C. The mixture is stirred for 15 min. Each of the reagents, chloriodomethane (0.70 ml, 0.010 mol) and n-butyllithium (5 ml, 0.008 mol) are added 4 more times over 45 min. at -75°C. The cooling bath is then removed and the solution warmed to 22°C over 1.5 hr.

35 The mixture is poured into 300 ml of saturated aq.

ammonium chloride solution. The tetrahydrofuran layer is separated. The aqueous phase is extracted with ethyl acetate (1 x 300 ml). The combined organic layers are washed with brine, dried over magnesium sulfate, filtered and concentrated to give a brown oil (27.4 g). The product could be used in the next step without purification. The desired diastereomer can be purified by recrystallization at a subsequent step.

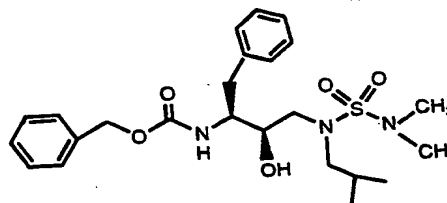
Alternately, the product could be purified by chromatography.

Example 3



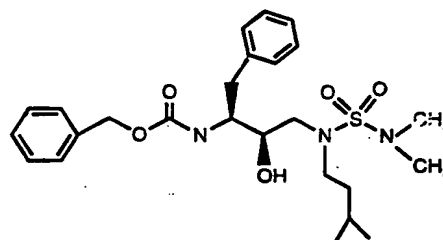
Preparation of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenyl]N-isobutylamine

A solution of N-benzyloxycarbonyl-3(S)-amino-1,2-(S)-epoxy-4-phenyl butane (50.0 g, 0.168 mol) and isobutylamine (246 g, 3.24 mol, 20 equivalents) in 650 mL of isopropyl alcohol was heated to reflux for 1.25 hours. The solution was cooled to room temperature, concentrated in vacuo and then poured into 1 L of stirring hexane whereupon the product crystallized from solution. The product was isolated by filtration and air dried to give 57.56 g, 92% of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenyl]N-isobutylamine, mp 108.0-109.5 °C, MH<sup>+</sup> m/z=371.

Example 4

5 Preparation of phenylmethyl[2R-hydroxy-3-  
[[[(dimethylamino)sulfonyl](2-methylpropyl)amino]-1S-  
(phenylmethyl)propyl]carbamate

10 The product from Example 3 (740 mg, 2.0 mmol) and  
diisopropylethylamine (382  $\mu$ L, 2.2 mmol) were dissolved in  
dichloromethane (1.5 mL) at room temperature. To this was  
added dimethylsulfamoyl chloride (354  $\mu$ L, 3.3 mmol). The  
reaction was stirred for 24 hours. The reaction mixture was  
15 chromatographed on silica gel (50 gm) using 1% ethanol in  
chloroform. The product fractions were pooled and  
concentrated to an oil. Anal. Calcd for  $C_{24}H_{35}N_3O_5S$ :  
C, 60.35; H, 7.39; N, 8.80. Found: C, 60.18; H, 7.40;  
N, 8.55.

Example 5

5 Preparation of phenylmethyl[2R-hydroxy-3-  
[[[(dimethylamino)sulfonyl](3-methylbutyl)amino]-1S-  
(phenylmethyl)propyl]carbamate

Part A

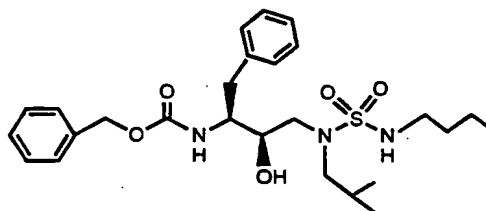
10 The procedure described in Example 1 was used to prepare N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]-N-[(3-methylbutyl)amine].

Part B

15 The product from Part A (192 mg, 0.5 mmol) and diisopropylethylamine (96 uL, 0.55 mmol) were dissolved in dichloromethane (10 mL) at room temperature. To this was added dimethylsulfonyl chloride (59 uL, 0.55 mmol). The reaction was stirred for 120 hours, then concentrated on a rotary evaporator. The residue was chromatographed on silica gel (50 gm) using 2% methanol in dichloromethane. The product fractions were pooled and concentrated to an oil which solidified on standing. Anal. Calcd for  $C_{25}H_{37}N_3O_5S$ . 0.9  $H_2O$ : C, 59.13; H, 7.64; N, 8.27; S, 6.31. Found:

25 C, 58.81; H, 7.38; N, 8.62; S, 6.70.



Example 6

5 Preparation of phenylmethyl 1-[[3-[[1-(butylamino)sulfonyl]-2-  
methylpropyl]amino]-2R-hydroxy-1S-(phenylmethyl)propyl]  
carbamate

10 Part A:

To a stirred solution of 3.88 gm (2 mL) of 30%  
fuming sulfuric acid in nitromethane (10mL) was added  
dropwise n-butylisocyanate (3.83 mL, 34 mmoles) at 0 C.  
After the addition was completed, the suspension was heated  
15 in an oil bath at 120 C. for 30 min. The reaction was  
cooled and filtered. The collected sulfamic acid crystals  
were air dried, wt. 4.73 gm (91%).

20 Part B:

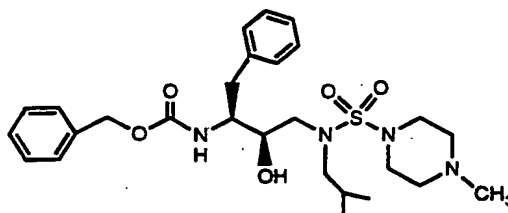
A suspension of n-butyl sulfamic acid (1.92 gm,  
12.53 mmoles) and phosphorus pentachloride (2.61 gm, 12.53  
mmoles) in benzene (20 mL) was warmed gently to initiate gas  
evolution. The reaction mixture was stirred at room  
25 temperature for 0.5 h., during which time a cloudy solution  
resulted. The cloudy solution was heated to reflux for 0.5  
h., then was concentrated. The product n-butyl sulfamoyl  
chloride was isolated by vacuum distillation (120 C., 300  
millitorr), 730 mg (liq.) (34%).

30

Part C:

The amine alcohol from Example 3 (370 mg, 1 mmole) was dissolved in 3 mL of dichloromethane and treated with diisopropylethylamine (278 uL, 2 mmoles), followed by chlorotrimethylsilane (126 uL, 1 mmole). The reaction mixture was stirred at r.t. for 1 h. n-Butyl sulfamoyl chloride from Part B (171 mg, 1 mmole) was added and the mixture was stirred at r.t. overnight. After removal of dichloromethane the oily residue was taken up in ethyl acetate and washed successively with 5% citric acid, saturated sodium bicarbonate, brine, dried over sodium sulfate and the solvent was evaporated to give 512 mg of product (oil).

The oily product (510 mg) was dissolved in dichloromethane (3 mL) and was treated with 2 mL of 4N HCl in dioxane. After 15 min. methanol (5 mL) was added and the solution was stirred for an additional 15 min. Solvent and excess reagent were evaporated. The product was isolated by silica gel chromatography to give 357 mg of phenylmethyl [3-[[[(butylamino)sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl] carbamate. Anal. Calcd for C<sub>26</sub>H<sub>39</sub>N<sub>3</sub>O<sub>5</sub>S: C, 61.76; H, 7.77; N, 8.31. Found: C, 61.89; H, 7.66; N, 8.18.

Example 7

5 Preparation of phenylmethyl [2R-hydroxy-3-[[4-methyl-1-  
piperazinyl)sulfonyl](2-methylpropyl)amino]-1S-  
(phenylmethyl)propyl] carbamate

Part A:

10

1-methylpiperazine hydrochloride (3.46 gm, 20  
 mmoles) was added in portions within 15 min. to a stirred  
 solution of sulfonyl chloride (8.99 gm, 67 mmoles) in  
 acetonitrile (40 mL). The suspension was gradually warmed to  
 15 reflux and maintained at reflux temperature overnight. A  
 brown solution was obtained. After cooling to r.t., the  
 crystals were collected by filtration, wt. 2.3 gm. A sample  
 of 4-methyl-1-piperazine sulfamoyl chloride.HCl was  
 recrystallized from methanol. Anal. Calcd. for  
 20 C<sub>5</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>Cl<sub>2</sub>S: C, 25.54; H, 5.14; N, 11.91; Cl, 30.16.  
 Found: C, 25.54; H, 4.91; N, 11.91; Cl, 29.88.

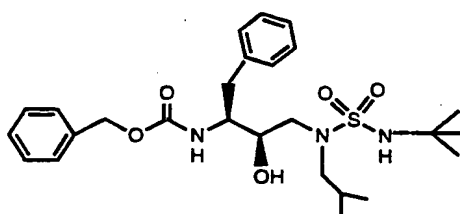
Part B:

25

N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-  
 phenylbutyl]-N-isobutylamine (370 mg, 1.0 mmole), prepared  
 according to the procedure in Example 3 was mixed with DIEA  
 (280 uL, 2.0 mmoles) and 4-methyl-1-piperazine sulfamoyl  
 chloride.HCl (240 mg, 1.0 mmole) in 6 mL of dichloromethane.  
 30 The reaction mixture was stirred for 5 days. After

filtration, the filtrate was concentrated to an oil, which was taken up in ethyl acetate. The ethyl acetate solution was washed with sodium bicarbonate solution, brine and dried over sodium sulfate. After evaporation, phenylmethyl (2R-hydroxy-3-[[[4-methyl-1-piperazinyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl] carbamate was obtained (412 mg).

10

Example 8

Preparation of phenylmethyl (2R-hydroxy-3-[[[4-methyl-1-dimethyl)aminosulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl] carbamate

Part A:

A 25 mL two-necked RB flask, equipped with a reflux condenser and dropping funnel and under a nitrogen atmosphere, was charged with t-butanol (207  $\mu$ L, 2.2 mmol) and 5 mL of hexane. Chlorosulfonyl isocyanate (192  $\mu$ L, 2.2 mmol) in 3 mL of hexane was added dropwise. Upon warming a homogeneous solution was obtained. The solution was heated at gentle reflux for 45 min., then was cooled to r.t. Solvent was removed under a steady stream of nitrogen. The crude t-butyl sulfamoyl chloride (a liquid) was used without further purification.

30

Part B:

N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]-N-isobutylamine (370 mg, 1.0 mmole), prepared  
5 according to the procedure in Example 3 was mixed with DIEA  
(139 uL, 1 mmole) in 5 mL of dichloromethane.  
Chlorotrimethylsilane (126 uL, 1 mmole) was added. After 1  
h., additional DIEA (160 uL) was added, followed by a  
dichloromethane solution (5mL) containing 1.1 mmole of  
10 t-butyl sulfamoyl chloride from Part A. The reaction  
mixture was stirred for 2 days. Solvent was removed under  
aspirator pressure. The oily residue was taken up in ethyl  
acetate and washed with 5% citric acid, saturated sodium  
bicarbonate, brine, dried over sodium sulfate and evaporated  
15 to an oily residue (380 mg).

The crude product was stirred in 4N HCl in  
dioxane (6 mL) for 15 min. After the addition of 4 mL of  
methanol to the reaction mixture, the solution was stirred  
20 for an additional 15 min, then concentrated to an oily  
residue. The product, phenylmethyl [2R-hydroxy-3-[[1,1-  
dimethylethyl)amino)sulfonyl](2-methylpropyl)amino]-1S-  
(phenylmethyl)propyl] carbamate was obtained after silica  
gel chromatography (188 mg, 37%). MS (MH)<sup>+</sup> = 506.  
25

Example 9

Preparation of phenylmethyl [2R-hydroxy-3-  
[[1(piperidyl)sulfonyl](2-methylpropyl)amino]-1S-  
30 (phenylmethyl)propyl]carbamate

Part A:

The product of Example 3 (750 mg, 2.02 mmol) and  
35 triethylamine (280 uL, 2.02 mmol) were dissolved in

dichloromethane (8.0 mL) at room temperature. To this was added piperidinesulfamoyl chloride (371 mg, 2.02 mmol). The reaction was stirred for 72 hours and then concentrated. The residue was chromatographed on silica gel (50 gm) using 5% methanol in dichloromethane. The product fractions were pooled and concentrated to an oil, 945 mg. TLC (silica / 5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) showed two spots. Rechromatographed. Anal. Calcd for C<sub>27</sub>H<sub>39</sub>N<sub>3</sub>O<sub>5</sub>S: C, 62.63; H, 7.51; N, 8.06. Found: C, 62.64; H, 7.59; N, 8.12.

Part B:

The product of Part A (430 mg) was combined with 10% Pd/C in methanol (10 mL) and hydrogenated at 5 psi for 1.4 hours at room temperature. The catalyst was removed by filtration and the solvent evaporated to afford the product as an oil, 305 mg.

Part C:

To a solution of Cbz-L-t-leucine (236 mg, 0.89 mmol) in DMF (2 mL) was added HOBt (115 mg, 0.85 mmol) and EDC (163 mg, 0.85 mmol). The reaction was stirred at room temperature for 1 hour and then a solution of the product from part B (305 mg, 0.79 mmol) in DMF (2 mL) was added. The reaction was stirred for 18 hours then concentrated. The residue was taken up in ethyl acetate and washed with 0.5% HCl solution, saturated aqueous NaHCO<sub>3</sub>, and saturated aqueous NaCl (50 mL each). The organic solution was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to a foam, 410 mg. <sup>1</sup>H NMR supports product.

Part D:

The product of Part C (410 mg) was combined with 10% Pd/C in methanol (10 mL) and hydrogenated at 5 psi for 2.0 hours at room temperature. The catalyst was removed by filtration and the solvent evaporated to afford the product as an foam, 320 mg.

Part E:

10

To a solution of the product of Part D (310 mg, 0.62 mmol) in dichloromethane (10 mL) was added diisopropylethylamine (130 uL, 0.75 mmol) and chloroacetic anhydride (117 mg, 0.68 mmol) at 0 C. The reaction was allowed to warm to room temperature and stir one hour. The solvent was removed and the residue taken up in ethyl acetate (50 mL). The organic solution was washed with 5% citric acid, saturated NaHCO<sub>3</sub>, and saturated NaCl (50 mL each). The solution was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to give a solid, 350 mg.

Part F:

The product of Part E (350 mg, 0.61 mmol) was combined with 40% aqueous dimethylamine (380 uL, 3.05 mmol) in isopropanol (10 mL). The reaction was stirred for 18 hours then concentrated. The residue was taken up in ethyl acetate (50 mL) and washed with water, saturated NaHCO<sub>3</sub>, and saturated NaCl (50 mL each). The solution was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to a solid. The solid was chromatographed on silica gel using 2% MeOH in dichloromethane. The product fractions were pooled and concentrated to give a white solid. Anal. Calcd for C<sub>29</sub>H<sub>51</sub>N<sub>5</sub>O<sub>5</sub>S. 0.25 H<sub>2</sub>O: C, 59.41; H, 8.77; N, 11.94. Found: C, 59.35; H, 8.78; N, 11.63.

Example 10

Following the procedures of the previous Examples 1-9, the intermediate compounds set forth in  
5 Tables 1A, 1B and 1C were prepared.

TABLE 1A

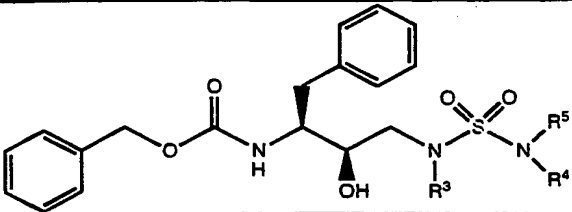
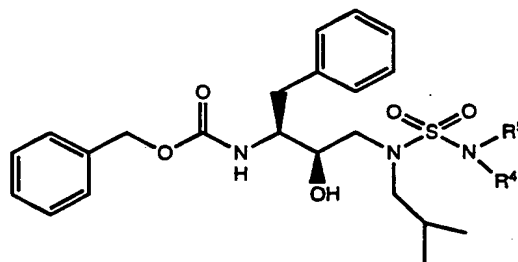
10			
	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>
	isobutyl	CH <sub>3</sub>	CH <sub>3</sub>
	isoamyl	CH <sub>3</sub>	CH <sub>3</sub>
	isobutyl	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	H
15	isobutyl	C(CH <sub>3</sub> ) <sub>3</sub>	H



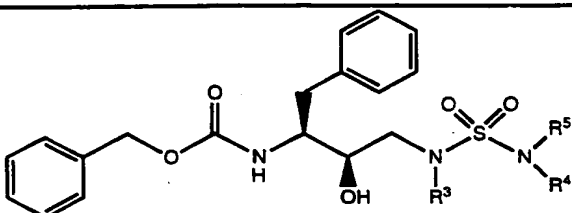
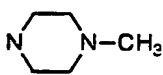


TABLE 1B



5

Entry	R <sup>4</sup>	R <sup>5</sup>
1	CH <sub>3</sub>	CH <sub>3</sub>
2	H	CH <sub>3</sub>
10 3	H	(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>
4	H	CH(CH <sub>3</sub> ) <sub>2</sub>
5	H	C(CH <sub>3</sub> ) <sub>3</sub>
6	H	cyclohexyl
7	R <sup>4</sup> & R <sup>5</sup> = pyrrolidinyl	

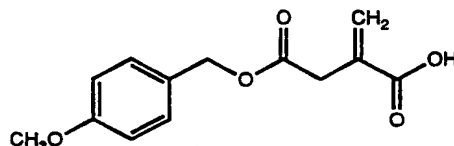
TABLE 1C

				
Entry	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	
5	A	isobutyl	methyl	H
	B	p-fluorobenzyl	methyl	methyl
10	C	isobutyl	isopropyl	H
	D	isobutyl	NR <sup>4</sup> R <sup>5</sup> =	
	E	isobutyl	phenyl	H
15	F	isobutyl	NR <sup>4</sup> R <sup>5</sup> =	
	G	isobutyl	NR <sup>4</sup> R <sup>5</sup> =	
20	H	benzyl	t-butyl	H
	I	cyclohexylmethyl	t-butyl	H
	J	isobutyl	C(CH <sub>3</sub> ) <sub>2</sub> CO <sub>2</sub> Me	H
25	K	cyclohexyl	t-butyl	H
	L	isobutyl	(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H
30	M	isobutyl	cyclohexyl	H

The following Examples 11-13 illustrate preparation of  $\beta$ -amino acid intermediates. These intermediates can be coupled to the intermediate compounds of Examples 1-10 to produce inhibitor compounds of the present invention containing  $\beta$ -amino acids.

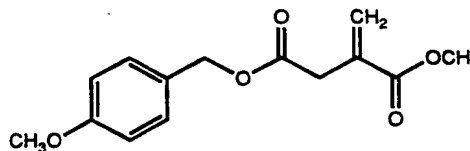
Example 11

A. Preparation of 4(4-methoxybenzyl)itaconate



A 5 L three-necked round bottomed flask equipped with constant pressure addition funnel, reflux condenser, nitrogen inlet, and mechanical stirrer was charged with itaconic anhydride (660.8g, 5.88 mol) and toluene (2300 mL). The solution was warmed to reflux and treated with 4-methoxybenzyl alcohol (812.4g, 5.88 mol) dropwise over a 2.6h period. The solution was maintained at reflux for an additional 1.5h and then the contents were poured into three 2 L erlenmeyer flasks to crystallize. The solution was allowed to cool to room temperature whereupon the desired mono-ester crystallized. The product was isolated by filtration on a Buchner funnel and air dried to give 850.2g, 58% of material with mp 83-85°C, a second crop, 17% was isolated after cooling of the filtrate in an ice bath.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 300 MHz 7.32(d,  $J=8.7$  Hz, 2H), 6.91(d,  $J=8.7$  Hz, 2H), 6.49(s, 1H), 5.85(s, 1H), 5.12(s, 2H), 3.83(s, 3H), 3.40(s, 2H).

## B. Preparation of Methyl 4(4-methoxybenzyl) itaconate

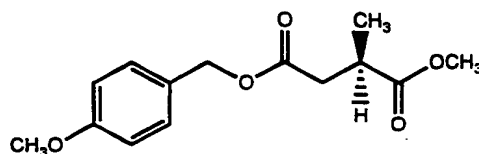


5 A 5 L three-necked round bottomed flask  
equipped with reflux condenser, nitrogen inlet, constant  
pressure addition funnel and mechanical stirrer was  
charged with 4(4-methoxybenzyl) itaconate (453.4g, 1.81  
mol) and treated with 1,5-diazabicyclo[4.3.0]non-5-ene  
10 (275.6g, 1.81 mol), (DBN), dropwise so that the  
temperature did not rise above 15°C. To this stirring  
mixture was added a solution of methyl iodide (256.9g,  
1.81 mol) in 250 mL of toluene from the dropping funnel  
over a 45m period. The solution was allowed to warm to  
15 room temperature and stirred for an additional 3.25h.

The precipitated DBN hydroiodide was removed by  
filtration, washed with toluene and the filtrate poured  
into a separatory funnel. The solution was washed with  
20 sat. aq. NaHCO<sub>3</sub> (2 X 500 mL), 0.2N HCl (1 X 500 mL), and  
brine (2 X 500 mL), dried over anhyd. MgSO<sub>4</sub>, filtered,  
and the solvent removed in vacuo. This gave a clear  
colorless oil, 450.2g, 94% whose NMR was consistent with  
the assigned structure. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 300 MHz 7.30(d,  
25 J=8.7 Hz, 2H), 6.90(d, J=8.7 Hz, 2H), 6.34(s, 1H),  
5.71(s, 1H), 5.09(s, 2H), 3.82(s, 3H), 3.73(s, 3H),  
3.38(s, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) 170.46, 166.47, 159.51,  
133.55, 129.97, 128.45, 127.72, 113.77, 66.36, 55.12,  
51.94, 37.64.

30

C. Preparation of Methyl 4(4-methoxybenzyl) 2(R)-methylsuccinate



5

A 500 mL Fisher-Porter bottle was charged with methyl 4(4-methoxybenzyl) itaconate (71.1g, 0.269 mol), rhodium (R,R) DiPAMP catalyst (204mg, 0.269 mmol, 0.1 mol%) and degassed methanol (215 mL). The bottle was  
10 flushed 5 times with nitrogen and 5 times with hydrogen to a final pressure of 40 psig. The hydrogenation commenced immediately and after ca. 1h the uptake began to taper off, after 3h the hydrogen uptake ceased and the bottle was flushed with nitrogen, opened and the contents  
15 concentrated on a rotary evaporator to give a brown oil that was taken up in boiling iso-octane (ca. 200 mL, this was repeated twice), filtered through a pad of celite and the filtrate concentrated in vacuo to give 66.6g, 93% of a clear colorless oil, <sup>1</sup>H NMR (CDCl<sub>3</sub> 300 MHz 7.30(d,  
20 J=8.7 Hz, 2H), 6.91(d, J=8.7 Hz, 2H), 5.08(s, 2H), 3.82(s, 3H), 3.67(s, 3H), 2.95(ddq, J=5.7, 7.5, 8.7 Hz, 1H), 2.79(dd, J=8.1, 16.5 Hz, 1H), 2.45(dd, J=5.7, 16.5 Hz, 1H), 1.23(d, J=7.5 Hz, 3H).

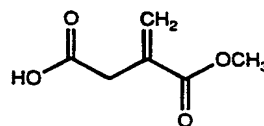
25 D. Preparation of Methyl 2(R)-methylsuccinate

A 3 L three-necked round-bottomed flask equipped with a nitrogen inlet, mechanical stirrer, reflux condenser and constant pressure addition funnel  
30 was charged with methyl 4(4-methoxybenzyl) 2(R)-methylsuccinate (432.6g, 1.65 mol) and toluene (1200 mL). The stirrer was started and the solution treated with trifluoroacetic acid (600 mL) from the dropping funnel

over 0.25h. The solution turned a deep purple color and the internal temperature rose to 45°C. After stirring for 2.25h the temperature was 27°C and the solution had acquired a pink color. The solution was concentrated on a rotary evaporator. The residue was diluted with water (2200 mL) and sat. aq. NaHCO<sub>3</sub> (1000 mL). Additional NaHCO<sub>3</sub> was added until the acid had been neutralized. The aqueous phase was extracted with ethyl acetate (2 X 1000 mL) to remove the by-products and the aqueous layer was acidified to pH=1.8 with conc. HCl. This solution was extracted with ethyl acetate (4 X 1000 mL), washed with brine, dried over anhyd. MgSO<sub>4</sub>, filtered and concentrated on a rotary evaporator to give a colorless liquid 251g, >100% that was vacuum distilled through a short path apparatus cut 1: bath temperature 120°C @ >1mm, bp 25-29°C; cut 2: bath temperature 140°C @ 0.5mm, bp 95-108°C, 151g, [α]<sub>D</sub> @ 25°C=+1.38°C(c=15.475, MeOH), [α]<sub>D</sub> =+8.48°C (neat); cut 3: bath temperature 140°C, bp 108°C, 36g, [α]<sub>D</sub> @ 25°C=+1.49°C(c=15.00, MeOH), [α]<sub>D</sub> =+8.98°C (neat). Cuts 2 and 3 were combined to give 189g, 78% of product, <sup>1</sup>H NMR (CDCl<sub>3</sub>) 300 MHz 11.6(brs, 1H), 3.72(s, 3H), 2.92(ddq, J=5.7, 6.9, 8.0 Hz, 1H), 2.81(dd, J=8.0, 16.8 Hz, 1H), 2.47(dd, J=5.7, 16.8 Hz, 1H), 1.26(d, J=6.9 Hz, 3H).

25

#### E. Preparation of Methyl Itaconate



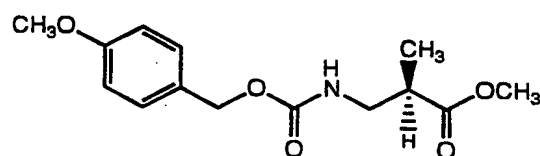
30

A 50 mL round bottomed flask equipped with reflux condenser, nitrogen inlet and magnetic stir bar was charged with methyl 4(4-methoxybenzyl) itaconate (4.00g, 16 mmol), 12 mL of toluene and 6 mL of trifluoroacetic acid. The solution was kept at room

temperature for 18 hours and then the volatiles were removed in vacuo. The residue was taken up in ethyl acetate and extracted three times with saturated aqueous sodium bicarbonate solution. The combined aqueous  
5 extract was acidified to pH=1 with aqueous potassium bisulfate and then extracted three times with ethyl acetate. The combined ethyl acetate solution was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated  
10 in vacuo. The residue was then vacuum distilled to give 1.23g, 75% of pure product, bp 85-87 @ 0.1 mm. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 300 MHz 6.34(s, 1H), 5.73(s, 2H), 3.76(s, 3H), 3.38(s, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) 177.03, 166.65, 129.220, 132.99, 52.27, 37.46.

15

F. Curtius Rearrangement of Methyl 2(R)-methylsuccinate: Preparation of Methyl N-Moz- $\alpha$ -methyl  $\beta$ -alanine.

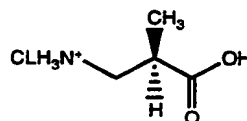


20

A 5L four necked round bottomed flask equipped with a nitrogen inlet, reflux condenser, mechanical stirrer, constant pressure addition funnel, and  
25 thermometer adapter was charged with methyl 2(R)-methylsuccinate (184.1g, 1.26 mol), triethylamine (165.6g, 218 mL, 1.64 mol, 1.3 equivalents), and toluene (1063 mL). The solution was warmed to 85°C and then treated dropwise with a solution of diphenylphosphoryl  
30 azide (346.8g, 1.26 mol) over a period of 1.2h. The solution was maintained at that temperature for an additional 1.0h and then the mixture was treated with 4-methoxybenzyl alcohol (174.1g, 1.26 mol) over a 0.33h

period from the dropping funnel. The solution was stirred at 88°C for an additional 2.25h and then cooled to room temperature. The contents of the flask were poured into a separatory funnel and washed with sat. aq. NaHCO<sub>3</sub> (2 X 500 mL), 0.2N HCl (2 X 500 mL), brine (1 X 500 mL), dried over anhyd. MgSO<sub>4</sub>, filtered, and concentrated in vacuo to give 302.3g, 85% of the desired product as a slightly brown oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 300 MHz 7.32(d, J=8.4 Hz, 2H), 6.91(d, J=8.4 Hz, 2H), 5.2(brm, 1H), 5.05(s, 2H), 3.83(s, 3H), 3.70(s, 3H), 3.35(m, 2H), 2.70(m, 2H), 1.20(d, J=7.2 Hz, 3H).

G. Hydrolysis of Methyl N-Moz-α-methyl β-alanine:  
Preparation of α-methyl β-alanine Hydrochloride



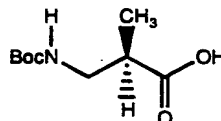
A 5 L three-necked round bottomed flask equipped with a reflux condenser, nitrogen inlet and mechanical stirrer was charged with methyl N-Moz-α-methyl β-alanine (218.6g, 0.78 mol), glacial acetic acid (975 mL) and 12N hydrochloric acid (1960 mL). The solution was then heated to reflux for 3h. After the solution had cooled to room temperature (ca. 1h) the aqueous phase was decanted from organic residue (polymer) and the aqueous phase concentrated on a rotary evaporator. Upon addition of acetone to the concentrated residue a slightly yellow solid formed that was slurried with acetone and the white solid was isolated by filtration on a Buchner funnel. The last traces of acetone were removed by evacuation to give 97.7g, 90% of pure product, mp 128.5-130.5°C [ $\alpha$ ]<sub>D</sub> @ 25°C=9.0°C (c=2.535, Methanol). <sup>1</sup>H NMR (D<sub>2</sub>O) 300 MHz 3.29(dd, J=8.6, 13.0 Hz, 1H), 3.16(dd, J=5.0, 13.0m Hz,



1H), 2.94(ddq, J=7.2, 5.0, 8.6 Hz, 1H), 1.30(d, J=7.2 Hz, 3H); <sup>13</sup>C NMR (D<sub>2</sub>O) 180.84, 44.56, 40.27, 17.49.

#### H. Preparation of N-Boc α-Methyl β-Alanine

5



A solution of α-methyl β-alanine hydrochloride (97.7g, 0.70 mol) in water (1050 mL) and dioxane (1050 mL) the pH was adjusted to 8.9 with 2.9N NaOH solution. This stirring solution was then treated with di-tert-butyl pyrocarbonate (183.3g, 0.84 mol, 1.2 equivalents) all at once. The pH of the solution was maintained between 8.7 and 9.0 by the periodic addition of 2.5N NaOH solution. After 2.5h the pH had stabilized and the reaction was judged to be complete. The solution was concentrated on a rotary evaporator (the temperature was maintained at <40°C). The excess di-tert-butyl pyrocarbonate was removed by extraction with dichloromethane and then the aqueous solution was acidified with cold 1N HCl and immediately extracted with ethyl acetate (4 X 1000 mL). The combined ethyl acetate extract was washed with brine, dried over anhyd. MgSO<sub>4</sub>, filtered and concentrated on a rotary evaporator to give a thick oil 127.3g, 90% crude yield that was stirred with n-hexane whereupon crystals of pure product formed, 95.65g, 67%, mp 76-78°C, [α]<sub>D</sub> @ 25°C=-11.8°C (c=2.4, EtOH). A second crop was obtained by concentration of the filtrate and dilution with hexane, 15.4g, for a combined yield of 111.05g, 78%. <sup>1</sup>H NMR (acetone D<sub>6</sub>) 300 MHz 11.7 (brs, 1H), 6.05 (brs 1H), 3.35 (m, 1H), 3.22 (m, 1H), 2.50 (m, 1H), 1.45(s, 9H), 1.19 (d, J=7.3 Hz, 3H); <sup>13</sup>C NMR (acetone D<sub>6</sub>) 177.01, 79.28, 44.44, 40.92, 29.08, 15.50. Elemental analysis calc'd. for C<sub>9</sub>H<sub>17</sub>NO<sub>4</sub>:

C, 53.19, H, 8.42; N, 6.89. Found: C, 53.36; H, 8.46; N, 6.99.

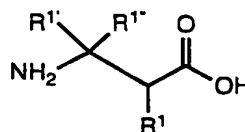
I. Preparation of N-4-Methoxybenzyloxycarbonyl  $\alpha$ -Methyl  
5  $\beta$ -Alanine

A solution of N-4-methoxybenzyloxycarbonyl  
 $\alpha$ -methyl  $\beta$ -alanine methyl ester (2.81g, 10.0 mmol) in 30  
10 mL of 25% aqueous methanol was treated with lithium  
hydroxide (1.3 equivalents) at room temperature for a  
period of 2h. The solution was concentrated in vacuo and  
the residue taken up in a mixture of water and ether and  
the phases separated and the organic phase discarded.  
The aqueous phase was acidified with aqueous potassium  
15 hydrogen sulfate to pH=1.5 and then extracted three times  
with ether. The combined ethereal phase was washed with  
saturated aqueous sodium chloride solution; dried over  
anhydrous magnesium sulfate, filtered and concentrated in  
vacuo to give 2.60 g, 97% of N-4-Methoxybenzyloxycarbonyl  
20  $\alpha$ -methyl  $\beta$ -alanine (N-Moz-AMBA) which was purified by  
recrystallization from a mixture of ethyl acetate and  
hexane to give 2.44g, 91% of pure product, mp 96-97°C,  
MH+=268.  $^1\text{H}$  NMR (D<sub>6</sub>-acetone/300 MHz) 1.16 (3H, d,  
J=7.2Hz), 2.70 (1H, m), 3.31 (2H, m), 3.31 (3H, s), 4.99  
25 (2H, s), 6.92 (2H, 4, J=8.7 Hz), 7.13 (2H, d, J=8.7 Hz).

Example 12

Following generally the procedure of Example 11, the  $\beta$ -amino acids set forth in Table 2 were prepared.

5

Table 2

10







Entry	R <sup>1</sup>	R <sup>1'</sup>	R <sup>1''</sup>
1	-CH <sub>3</sub>	H	H
15	2	-CH(CH <sub>3</sub> ) <sub>2</sub>	H
	3	-C(CH <sub>3</sub> ) <sub>3</sub>	H
	4	H	H
20	5	H	-CH <sub>3</sub>
	6	H	-CH <sub>3</sub>
	7	H	-CO <sub>2</sub> CH <sub>3</sub>
	8	H	-CONH <sub>2</sub>
	9	-CH <sub>2</sub> CH <sub>3</sub>	H
	10	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	H
	11	-CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H
25	12	-CH <sub>2</sub> -  -OH	H
	13	-CH <sub>2</sub> - 	H
	14	-CH <sub>2</sub> COOH	H
	15	H	-CH(CH <sub>3</sub> ) <sub>2</sub>
30	16	H	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>
	17	H	-CH <sub>2</sub> - 

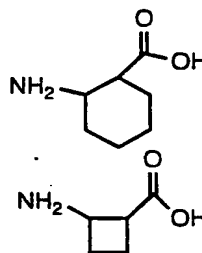
Table 2 (Cont'd)

Entry	R <sup>1</sup>	R <sup>1</sup>	R <sup>1</sup>
5			
18	H	-CH <sub>2</sub> CH <sub>2</sub> - 	H
19	H	-(CH <sub>2</sub> ) <sub>3</sub> - 	H
20	H	-(CH <sub>2</sub> ) <sub>4</sub> - 	H
21	H	-(CH <sub>2</sub> ) <sub>3</sub> CH(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	H

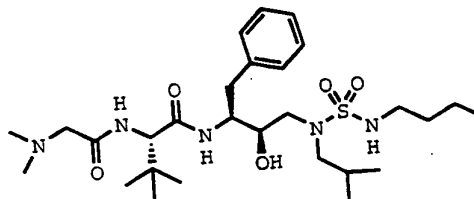
10

Example 13

15 Utilizing generally the procedure set forth in Example 11, the following  $\beta$ -amino acid compounds were prepared.



20

Example 14

5 Preparation of N-[3-[[[butylamino)sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[[2-(dimethylamino)-1-oxoethyl]aminodimethylbutanamide

10 Part A:

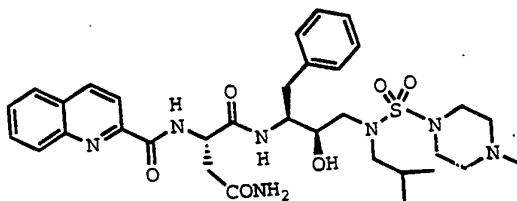
The product from Example 3 (357 mg, 0.71 mmol) in 10 mL of methanol was hydrogenated over 10% palladium on carbon (60 mg) for 5 hr. The mixture was then  
15 filtered through Celite and concentrated to give the product as an oil (213 mg).

Part B:

20 The free amine from Part A (210 mg, 0.566 mmol) was coupled with N-CBZ-L-t-butylglycine (180 mg, 0.679 mmol) in the presence of N-hydroxybenzotriazole (92 mg, 0.679 mmol) and EDC (130 mg, 0.679 mmol) to yield 275 mg  
25 of phenylmethyl [[[1S-[3-[(butylamino)sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-amino]carbonyl]-2,2-dimethylpropyl]carbamate after purification on silica column.

Part C:

The product from Part B (235 mg) in methanol was hydrogenated over 10% palladium on carbon (50 mg) for 4 h. The mixture was filtered through Celite and concentrated to give the product as an oil (173 mg, 0.369 mmol). This free amine was then dissolved in 3 mL of dichloromethane and acylated with bromo acetyl chloride (34 uL, 0.406 mmol) in the presence of DIEA (62 uL, 0.443 mmol) for 2 h. The crude mixture (190 mg, 0.32 mmol) was dissolved in 1 mL of isopropanol and mixed with a 40% wt dimethylamine in water (180 uL, 1.6 mmol) and stirred overnight. Solvent and excess reagents were evaporated. The oily residue was taken up in ethylacetate, washed with saturated sodium bicarbonate, brine and dried over sodium sulfate. The product N-[3-[[[butylamino)-sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[[2-(dimethylamino)-1-oxoethyl]amino]3,3-dimethylbutanamide was purified by silica gel chromatography. Anal. Calc'd for C<sub>28</sub>H<sub>51</sub>N<sub>5</sub>O<sub>5</sub>S. 0.5 H<sub>2</sub>O: C, 58.10; H, 9.06; N, 12.09. Found: C, 57.81; H, 8.44; N, 12.01. EI MS M<sup>+</sup> = 569.

Example 15

5 Preparation of N1-[2R-hydroxy-3-[[[4-methyl-1-piperazinyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide

10 Part A:

A solution of the carbamate from Example 7 (412 mg, 0.77 mmoles) containing 20 mL methanol and 5 mL acetic acid was hydrogenated over 10% palladium on carbon (80 mg) for 6 h. After filtration of the reaction mixture, the filtrate was evaporated to an oil. The oily residue was dissolved in ethyl acetate and washed with sodium bicarbonate solution. The organic layer was evaporated to give the free amine (100 mg).

20

Part B:

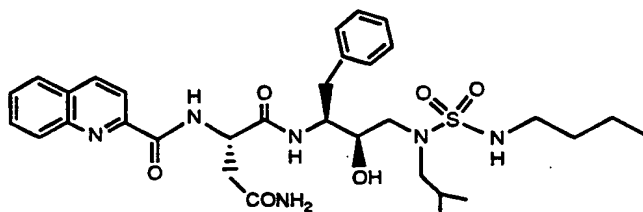
The free amine from Part A (80 mg, 0.20 mmoles) was coupled with N-BOC-L-asparagine (61 mg, 0.264 mmoles) in the presence of N-hydroxybenzotriazole (48mg, 0.35 mmoles) and EDC (50 mg, 0.264 mmoles) to yield 125 mg of N1[2R-hydroxy -3-[3-[[[4-methyl-1-piperazinyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]]-2S-[(1,1-dimethylethoxycarbonyl)amino]butane diamide.

30

Part C:

N1-[2R-hydroxy -3-[3-[(4-methyl-1-piperazinyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]]-2S-[(1,1-dimethylethoxycarbonyl)amino]butane diamide (118 mg, 0.19 mmole) was stirred in 4N HCl in dioxane (5 mL) at r.t. for 0.5 h. Solvent and excess reagent were evaporated to dryness. The product was dried in vacuo. This material (116 mg, 0.19 mmole) was then reacted with 2-quinoline carboxylic acid N-hydroxysuccinimide ester (53 mg, 0.19 mmole), DIEA (83  $\mu$ L, 0.60 mmole) in DMF (1 mL) overnight. The product N1-[2R-hydroxy -3-[3-[(4-methyl-1-piperazinyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamid was purified by silica gel chromatography. Anal. Calcd for  $C_{33}H_{45}N_7O_6S$ .  $0.5 H_2O/0.3 CH_3CH_2OCH_2CH_3$ : C, 58.76; H, 7.06; N, 14.03. Found: C, 58.23; H, 6.98; N, 13.81.



Example 16

5 Preparation of N1-[3-[[[(butylamino)sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butane]diamide

10 Part A:

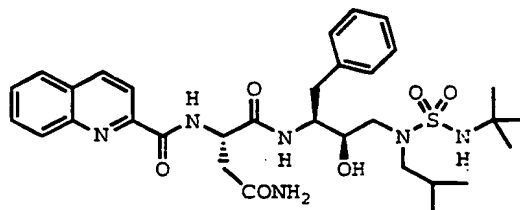
The procedures described in Example 6, Parts A-C, were used to prepare phenylmethyl [3-[[[(butylamino)sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl] carbamate. A methanolic solution of this carbamate (460 mg, 0.796 mmol) was hydrogenated over 10% palladium on carbon (90 mg) to give the free amine (329 mg).

20 Part B:

The free amine from Part A (266 mg, 0.6 mmol) was coupled with N-BOC-L-asparagine (167 mg, 0.72 mmol) in the presence of N-hydroxybenzotriazole (130 mg, 0.96 mmol) and EDC (138 mg, 0.72 mmol) to yield 306 mg of N1[2R-hydroxy-3-[[[(butylamino)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2S-[(1,1-dimethylethoxycarbonyl)amino]butane]diamide after purification on a silica column.

Part C:

N1[2R-hydroxy -3-[3-  
[(butylamino)sulfonyl](2-methylpropyl)amino]-1S-  
5 (phenylmethyl)propyl]]-2S-[(1,1-  
dimethylethoxycarbonyl)amino]butane diamide (150 mg,  
0.26 mmoles) was stirred in 4N HCl in dioxane (4 mL) at  
r.t. for 0.5 h. Solvent and excess reagent were  
evaporated to dryness. The product was dried in vacuo.  
10 This material (140 mg, 0.26 mmoles) was then reacted  
with 2-quinoline carboxylic acid N-hydroxysuccimide  
ester (70 mg, 0.26 mmoles), DIEA (72 uL, 0.52 mmoles)  
in dichloromethane (2 mL) overnight. The product -N1-  
[3-[(butylamino)sulfonyl](2-methylpropyl)amino]-2R-  
15 hydroxy-1S-(phenylmethyl)propyl]-2S-[(2-  
quinolinylcarbonyl)amino]butanediamide was purified by  
silica gel chromatography. Anal. Calcd for  
C<sub>32</sub>H<sub>44</sub>N<sub>6</sub>O<sub>6</sub>S: C, 59.98; H, 6.92; N, 13.12. Found: C,  
59.98; H, 6.65; N, 12.72.

Example 17

5 Preparation of N1-[3-[[[(1,1-  
dimethylethyl)amino]sulfonyl](2-methylpropyl)amino]-2R-  
hydroxy-1S-(phenylmethyl)propyl]-2S-[(2-  
quinolinylcarbonyl)amino]butanediamide

10 Part A:

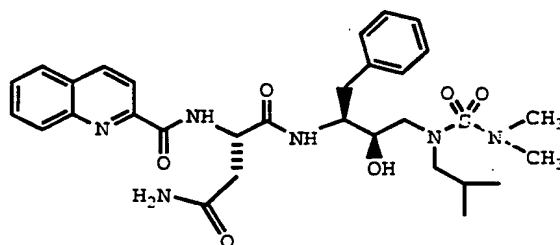
A 20 mL methanol solution of phenylmethyl [2R-  
hydroxy -3-[[[(1,1-dimethylethyl)sulfonyl](2-  
methylpropyl)amino]-1S-(phenylmethyl)propyl] carbamate  
15 from Example 8 (170 mg, 0.33 mmoles) was hydrogenated  
over 10% palladium on carbon (40 mg). The resulting  
free amine (110 mg, 0.30 mmole) was coupled with N-BOC-L-  
asparagine (84 mg, 0.36 mmoles) in the presence of N-  
hydroxybenzotriazole (65 mg, 0.48 mmoles) and EDC (69 mg,  
20 0.36 mmoles) to yield 160 mg of N1[2R-hydroxy -3-[3-  
[[[(1,1-dimethylethyl)amino]sulfonyl](2-  
methylpropyl)amino]-1S-(phenylmethyl)propyl]]-2S-[(1,1-  
dimethylethoxycarbonyl)amino]butane diamide.

25 Part B:

N1[2R-hydroxy -3-[3-[[[(1,1-  
dimethylethyl)amino]sulfonyl](2-methylpropyl)amino]-1S-  
(phenylmethyl)propyl]]-2S-[(1,1-  
30 dimethylethoxycarbonyl)amino]butane diamide (150 mg, 0.25  
mmole) was stirred in 4N HCl in dioxane (5 mL) at r.t.

for 0.5 h. Solvent and excess reagent were evaporated to dryness. The product was dried in vacuo. This material (135 mg, 0.25 mmoles) was then reacted with 2-quinoline carboxylic acid N-hydroxysuccinimide ester (70 mg, 0.25 mmoles), DIEA (72  $\mu$ L, 0.52 mmoles) in DMF (1 mL) overnight. The product N1-[3-[[[(1,1-dimethylethyl)amino]sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide was purified by silica gel chromatography (85 mg, 53%). Anal. Calcd for  $C_{32}H_{44}N_6O_6S$ . 0.8  $H_2O$ : C, 58.66; H, 7.02; N, 12.83. Found: C, 59.00; H, 6.84; N, 12.54.

#### Example 18



Preparation of N1-[3-[[[(N,N-dimethylamino)sulfonyl](3-methylbutyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide

#### Part A:

Preparation of N-3(S)-(Benzyloxycarbonyl)-amino-2(R)-hydroxy-4-phenylbutylamine, N-(3-methylbutyl). A solution of 20g (67 mmol) of N-benzyloxycarbonyl-3(S)-amino-1,2-(S)-epoxy-4-phenylbutane in 140 mL of isopropyl alcohol was treated with 83g (952 mmol) of isoamylamine and refluxed for one hour. The solution was cooled, concentrated, hexane added and the resulting solid filtered to afford 22.4g of the desired product.

Part B:

Preparation of N-3(S)-(Benzyloxycarbonyl)-amino-2(R)-hydroxy-4-phenylbutylamine, N-(3-methylbutyl)-N-(t-butyloxycarbonyl). To a solution of 22.4g (58.3 mmol) of product from Part A above, 6.48g (64.1 mmol) of triethylamine and 150 mg of N,N-dimethyl-4-aminopyridine in 200 mL of tetrahydrofuran at 0°C was added 12.7g (58.3 mmol) of di-t-butylpyrocarbonate in 10 mL of THF. After 3.5 hours at room temperature, the volatiles were removed, ethyl acetate added and washed with 5% citric acid, sat'd NaHCO<sub>3</sub>, dried and concentrated to afford 30g of crude product. Chromatography on silica gel using 20% ethyl acetate/hexane afforded 22.5g (79%) of the desired product.

Part C:

Preparation of N-3(S)-[N-benzyloxycarbonyl-L-asparaginyll]amino-2(R)-hydroxy-4-phenylbutylamine, N-(3-methylbutyl)-N-(t-butyloxycarbonyl). A solution of 22.5g of product from Part B above in 200 mL of ethanol was hydrogenated over 5.9g of 10% palladium-on-carbon under 50 psig hydrogen for one hour. The catalyst was filtered and the solvent removed under reduced pressure to afford 15.7g of free amine. This was dissolved in 130 mL of DMF and 4.54g (44.9 mmol) of N-methylmorpholine was added to a mixture of 13.3g (49.9 mmol) N-benzyloxy-carbonyl-L-asparagine, 11.5g (74.9 mmol) of N-hydroxybenzotriazole and 10.5g (54.9 mmol) of EDCI in 120 mL of DMF at 0°C, which had been preactivated for one hour prior to the addition. The mixture was stirred for 2 hours at 0°C and then for 12 hours at room temperature. The reaction was poured into 1L of sat'd aqueous sodium bicarbonate, the solid collected, dissolved in ethyl acetate, washed with water, sat'd sodium bicarbonate, 5% citric acid and

brine, dried and concentrated to afford 16.7g of the desired product.

Part D:

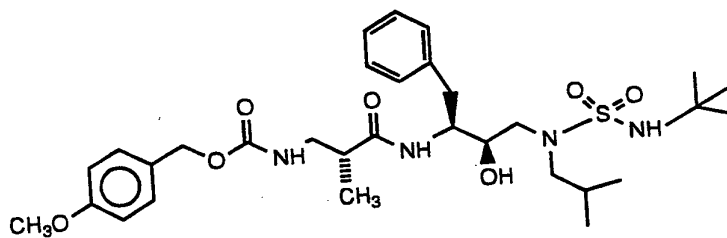
5 Preparation of N-3(S)-[N-(2-quinolinylcarbonyl)-L-asparaginyllamino-2(R)-hydroxy-4-phenylbutylamine, N-(3-methylbutyl)-N-(t-butyloxycarbonyl). A solution of 16.7g (28.0 mmol) of product from Part C in 250 mL of methanol was  
10 hydrogenated over 6.0g of 10% palladium-on-carbon and under 50 psig hydrogen for one hour. The catalyst was filtered and the solution concentrated to afford 10.0g of free amine. This was dissolved in 100 mL of methylene chloride, 4.35g (43 mmol) of N-methylmorpholine was  
15 added followed by 5.53g (20.5 mmol) of quinoline-2-carboxylic acid, N-hydroxysuccinimide ester. This was stirred at room temperature overnight, the solvent removed, ethyl acetate added and washed with 5% citric acid, sat'd sodium bicarbonate, brine, dried and  
20 concentrated to afford 14g of crude product. Recrystallization from ethyl acetate and hexane afforded 10.5g (83%) of desired product.

Part E:

25 Preparation of N-3(S)-[N-(2-quinolinyl-carbonyl)-L-asparaginyllamino-2(R)-hydroxy-4-phenylbutylamine, N-(3-methylbutyl). To 80 mL of 4N hydrochloric acid in dioxane was added 9.17g (14.8 mmol) of product from Part D above. After one hour, the  
30 product becomes gummy. The solvents were removed, diethyl ether added and removed and the residue dissolved in 20 mL of methanol. This solution was added to 400 mL of sat'd aqueous sodium bicarbonate, the solids  
35 collected, washed with acetone and hexane and dried in vacuo over P<sub>2</sub>O<sub>5</sub> to afford 4.75g of the desired product.

Part E:

To a solution of 200 mg (0.38 mmol) of the amino alcohol from Part E above in 10 mL of anhydrous tetrahydrofuran and 0.3 mL of N,N-dimethylformamide, was added 42 mg (0.42 mmol) of triethylamine and then 55 mg (0.38 mmol) of dimethylsulfamoyl chloride. After stirring from twenty hours at room temperature, the volatiles were removed in vacuo, ethyl acetate added and the solution washed with 5% aqueous citric acid, saturated aqueous sodium bicarbonate and saturated brine. The organic layer was dried and concentrated to afford 166 mg of crude product, which was chromatographed on silica gel using a gradient of 1-10% isopropanol in methylene chloride to afford 119 mg of pure product, m/e 627 (M+H). Calcd. for  $C_{31}H_{42}N_6O_6S$  627.2965, found 627.2998.

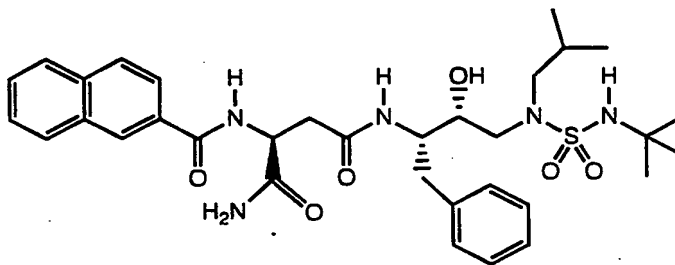
Example 19

Preparation of [(4-methoxyphenyl)methyl] [3-[[[3-[[[1,1-dimethylethyl]aminosulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]amino]-2R-methyl-3-oxopropyl]carbamate

To a solution of 83 mg (0.31 mmol) of N-(4-methoxy)benzyloxycarbonyl 2R-methyl-3-aminopropionic acid and 71 mg (0.46 mmol) of N-hydroxybenzotriazole in 2 mL of anhydrous N,N-dimethylformamide (DMF) at 0°C, was

added 65 mg (0.34 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After two hours at 0°C, a solution of 104 mg (0.28 mmol) of free amine from example 8, part C in 0.5 mL of DMF was added. After two hours at 0°C and fourteen hours at room temperature, the DMF was removed in vacuo, ethyl acetate added, washed with saturated aqueous sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 200 mg of crude material. This was chromatographed on silica gel using 3% methanol/methylene chloride to afford 120 mg of product, which was further purified by crystallization from diethyl ether/hexane to afford 25 mg (13%) of the desired product m/e = 627 (M+Li).

15

Example 20

20 Preparation of N4-[3-[[[(1,1-dimethylethyl)aminol-sulfonyl(2-methylpropyl)aminol-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[(2-quinoliny)lcarbonyl]-aminol]butanediamide

25 107 mg (0.37 mmol) of N-2-(quinoylcarbonyl)-L-isoasparagine and 76 mg (1.5 eq) of N-hydroxysuccinamide were dissolved in 2 mL of dimethylformamide and cooled to zero degrees C. To this was added 111 mg (0.37 mmol) of EDC and the solution stirred for 20 minutes. To this  
30 cooled solution was added 140 mg (0.37 mmol) of the free

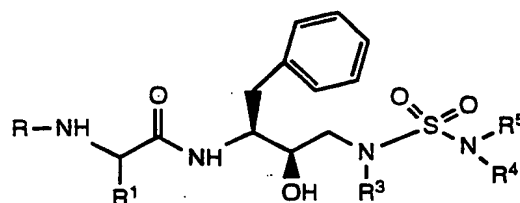


amine from example 8, part C and the reaction was returned to room temperature and stirred for 18 hours. The dimethylformamide was removed by evaporation and the residue was partitioned between ethyl acetate and  
5 saturated sodium bicarbonate. The organic layer was washed with 5%  $\text{KHSO}_4$  and brine, dried over magnesium sulfate, filtered and concentrated to yield 216 mg of crude solid, which was chromatographed using ethyl acetate:methanol:hexane, 95:5:50 to yield 110 mg (4.8%  
10 yield) of pure product,  $m/e = 641$  (M+H).

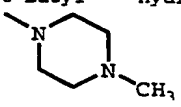
#### Example 21

Following the procedures of Examples 1-20, the  
15 compounds shown in Tables 3A and 3B were prepared.

TABLE 3a

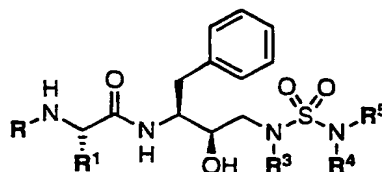


5


Entry No.	R	R1	R3	R4	R5
1	Cbz	t-Butyl	i-Amyl	Methyl	Methyl
10 2	Q	t-Butyl	i-Amyl	Methyl	Methyl
3	Cbz	i-Butyl	i-Butyl	Methyl	Hydrogen
4	N,N-Dimethylglycine	t-Butyl	i-Butyl	n-Butyl	Hydrogen
5	N,N-Dimethylglycine	t-Butyl	i-Butyl	Methyl	Hydrogen
6	Q	CH <sub>2</sub> C(O)NH <sub>2</sub>	i-Butyl	n-Butyl	Hydrogen
15 7	Q	CH <sub>2</sub> C(O)NH <sub>2</sub>	i-Butyl	t-Butyl	Hydrogen
8	Q	CH <sub>2</sub> C(O)NH <sub>2</sub>	i-Butyl		
9	Q	CH <sub>2</sub> C(O)NH <sub>2</sub>	i-Butyl	Phenyl	Hydrogen
10	Q	CH <sub>2</sub> C(O)NH <sub>2</sub>	i-Butyl	Cyclohexyl	Hydrogen

20

TABLE 3B

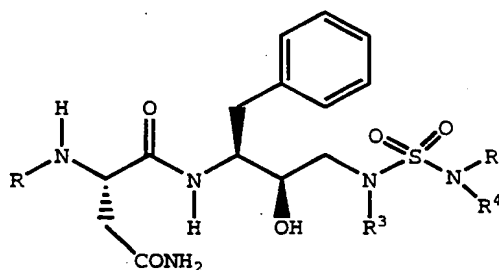


5

Entry	R	R1	R3	R4	R5
10	A	Cbz	t-butyl	isoamyl	methyl
	B	Cbz	t-butyl	isobutyl	methyl
	C	N,N-Dimethylglycine	t-butyl	isobutyl	methyl
15	D	Q	CH <sub>2</sub> CONH <sub>2</sub>	isobutyl	cyclohexyl
	E	Q	CH <sub>2</sub> CONH <sub>2</sub>	isobutyl	phenyl
20	F	N,N-Dimethylglycine	t-butyl	isobutyl	NR <sub>4</sub> R <sub>5</sub> = 

Utilizing the procedures set forth above, the compounds shown in Tables 4-14 could be prepared. Thus, utilizing the intermediates of Examples 1-10 according to the procedures in Examples 14-21, the compounds shown in Tables 4-16 could be prepared.

TABLE 4







Entry No.	R	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>
1	Cbz <sup>a</sup>	CH <sub>3</sub>	n-Butyl	CH <sub>3</sub>
2	Cbz	i-Butyl	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>
3	Cbz	i-Butyl	n-Butyl	H
4	Q <sup>b</sup>	i-Butyl	n-Butyl	H
5	Cbz	i-Propyl	n-Butyl	H
6	Q	i-Propyl	n-Butyl	CH <sub>3</sub>
7	Cbz	C <sub>6</sub> H <sub>5</sub>	n-Butyl	H
8	Cbz	-CH <sub>2</sub> - 	n-Butyl	H
9	Cbz	-CH <sub>2</sub> - 	n-Butyl	H
10	Q	-CH <sub>2</sub> - 	n-Butyl	H
11	Cbz	- 	n-Butyl	H
12	Cbz	i-Butyl	n-Propyl	H

TABLE 4 (Cont'd.)









Entry No.	R	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>
13	Cbz	i-Butyl	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	H
14	Cbz	(R)-CH(CH <sub>3</sub> )- 	n-Butyl	H
15	Cbz	CH <sub>2</sub> - 	i-Propyl	H
16	Cbz	-CH <sub>2</sub> - 	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	H
17	Cbz	i-Butyl	-CH <sub>2</sub> CH <sub>3</sub>	H
18	Cbz	i-Butyl	-CH(CH <sub>3</sub> ) <sub>2</sub>	H
19	Cbz	i-Butyl		H
20	Q	n-Butyl		H
21	Cbz	-CH <sub>2</sub> - 	-(CH <sub>2</sub> ) <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	H
22	Cbz	(CH <sub>2</sub> ) <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-CH(CH <sub>3</sub> ) <sub>2</sub>	H
23	Q	i-Butyl	-CH(CH <sub>3</sub> ) <sub>2</sub>	H
24	Cbz	i-Butyl	-C(CH <sub>3</sub> ) <sub>3</sub>	H
25	Q	i-Butyl	-C(CH <sub>3</sub> ) <sub>3</sub>	H
26	Cbz	-CH <sub>2</sub> - 	-C(CH <sub>3</sub> ) <sub>3</sub>	H
27	Q	-CH <sub>2</sub> - 	-C(CH <sub>3</sub> ) <sub>3</sub>	H
28	Cbz	-(CH <sub>2</sub> ) <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C(CH <sub>3</sub> ) <sub>3</sub>	CH <sub>3</sub>
29	Q	-(CH <sub>2</sub> ) <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C(CH <sub>3</sub> ) <sub>3</sub>	CH <sub>3</sub>
30	Cbz	-CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	-C(CH <sub>3</sub> ) <sub>3</sub>	H
31	Q	-CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	-C(CH <sub>3</sub> ) <sub>3</sub>	H
32	Cbz	-(CH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	-C(CH <sub>3</sub> ) <sub>3</sub>	CH <sub>3</sub>
33	Cbz	-(CH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	-C(CH <sub>3</sub> ) <sub>3</sub>	H
34	Cbz	n-Butyl	-C(CH <sub>3</sub> ) <sub>3</sub>	H

TABLE 4 (Cont'd.)







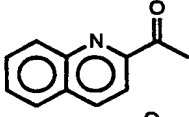
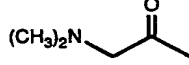
Entry No.	R	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>
35	Cbz	n-Pentyl	-C(CH <sub>3</sub> ) <sub>3</sub>	H
36	Cbz	n-Hexyl	-C(CH <sub>3</sub> ) <sub>3</sub>	H
37	Cbz	-CH <sub>2</sub> - 	-C(CH <sub>3</sub> ) <sub>3</sub>	H
38	Cbz	-CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>	-C(CH <sub>3</sub> ) <sub>3</sub>	H
39	Q	-CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>	-C(CH <sub>3</sub> ) <sub>3</sub>	H
40	Cbz	-CH <sub>2</sub> CH <sub>2</sub> -N 	-C(CH <sub>3</sub> ) <sub>3</sub>	H
41	Cbz	-CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> OCH <sub>3</sub> (para)	-C(CH <sub>3</sub> ) <sub>3</sub>	H
42	Cbz	-CH <sub>2</sub> - 	-C(CH <sub>3</sub> ) <sub>3</sub>	H
43	Cbz	-CH <sub>2</sub> - 	-C(CH <sub>3</sub> ) <sub>3</sub>	H
44	Cbz	-(CH <sub>2</sub> ) <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>	-C(CH <sub>3</sub> ) <sub>3</sub>	H
45	Q	-(CH <sub>2</sub> ) <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>	-C(CH <sub>3</sub> ) <sub>3</sub>	H
46	Cbz	-(CH <sub>2</sub> ) <sub>4</sub> OH	-C(CH <sub>3</sub> ) <sub>3</sub>	H
47	Q	-(CH <sub>2</sub> ) <sub>4</sub> OH	-C(CH <sub>3</sub> ) <sub>3</sub>	H
48	Q	-CH <sub>2</sub> - 	-C(CH <sub>3</sub> ) <sub>3</sub>	H
49	Q	-CH <sub>2</sub> - 	-C(CH <sub>3</sub> ) <sub>3</sub>	H
50	Cbz	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	H
51		-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	Me
52	(CH <sub>3</sub> ) <sub>2</sub> N 	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	H

TABLE 4 (Cont'd.)

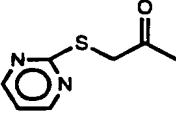
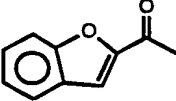
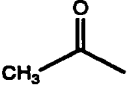
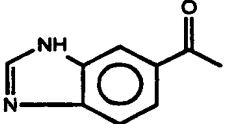
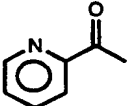
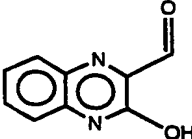
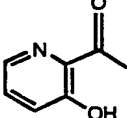
Entry No.	R	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>
53		-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	H
54		-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	H
55		-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	Me
56		-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	H
57		-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	Me
58		-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	Me
59		-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	H

TABLE 4 (Cont'd.)

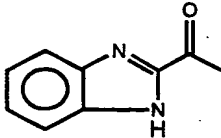
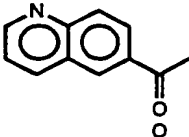
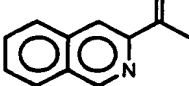
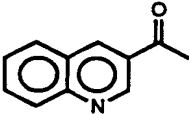
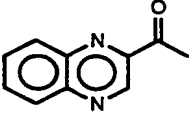
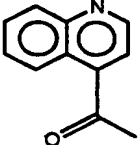
Entry No.	R	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>
60		-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	Me
61		-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	H
62		-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	H
63		-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	H
64		-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	Me
65		-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	H



TABLE 4 (Cont'd.)

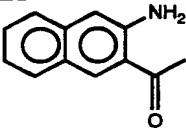
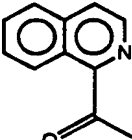
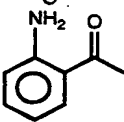
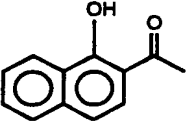


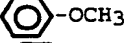

Entry No.	R	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>
66		-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	H
67		-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	H
68		-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	H
69		-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>	H
70	Q	-CH <sub>2</sub> Ph	-Ph	H
71	Q	-CH <sub>2</sub> - 	-Ph	H
72	Q	-CH <sub>2</sub> - 	-Ph	H
73	Q	-CH <sub>2</sub> - 	-Ph	H
74	Q	-CH <sub>2</sub> - 	-Ph	H

TABLE 4 (Cont'd.)











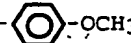






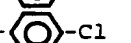


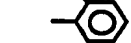

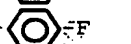
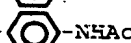




Entry No.	R	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>
75	Q	-CH <sub>2</sub> - 	-Ph	H
76	Q	-CH <sub>2</sub> CH=CH <sub>2</sub>	-Ph	H
77	Q	- 	-Ph	H
78	Q	- 	-Ph	H
79	Q	-CH <sub>2</sub> CH <sub>2</sub> Ph	-Ph	H
80	Q	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	-Ph	H
81	Q	-CH <sub>2</sub> CH <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	-Ph	H
82	Q	-CH <sub>2</sub> CH <sub>2</sub> -N 	-Ph	H
83	Q	-CH <sub>3</sub>	-Ph	H
84	Q	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> SCH <sub>3</sub>	-Ph	H
85	Q	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> S(O) <sub>2</sub> CH <sub>3</sub>	-Ph	H
86	Q	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	- 	H
87	Q	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-CH <sub>2</sub> - 	H
88	Q	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	H
89	Q	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-CH <sub>3</sub>	H
90	Q	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	- 	H
91	Q	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	- 	H
92	Q	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	- 	H
93	Q	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	- 	H

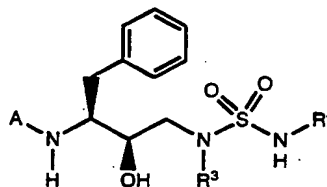
TABLE 4 (Cont'd.)

Entry No.	R	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>
94	Q	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>		H
95	Q	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>		H
96	Q	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>		H
97	Q	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>		H
98	Q	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>		H
99	Q	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>		H
100	Q	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>		H
101	Q	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>		H
102	Q	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>		H
103	Q	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>		H
104	Q	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>		H
105	Q	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>		H
106	Q	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>		H
107	Q	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>		H
108	Q	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>		H
109	Q	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>		H
110	Q	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>		H
111	Q	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>		H

a benzyloxycarbonyl

b 2-quinolinylcarbonyl

TABLE 5




Entry No.	A	R <sup>3</sup>	R <sup>4</sup>
1	Cbz-Val	i-amyl	-C <sub>6</sub> H <sub>5</sub>
2	Cbz-Leu	i-amyl	-C <sub>6</sub> H <sub>5</sub>
3	Cbz-Ile	i-amyl	-C <sub>6</sub> H <sub>5</sub>
4	Ac-D-homo-Phe	i-Bu	methyl
5	Qui-Orn(g-Cbz)	-CH <sub>2</sub> - 	-C <sub>6</sub> H <sub>5</sub>
6	Cbz-Asn	-CH <sub>2</sub> CH=CH <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>
7	Acetyl-t-BuGly	i-amyl	-C <sub>6</sub> H <sub>5</sub>
8	Acetyl-Phe	i-amyl	-C <sub>6</sub> H <sub>5</sub>
9	Acetyl-Ile	i-amyl	-C <sub>6</sub> H <sub>5</sub>
10	Acetyl-Leu	i-amyl	-C <sub>6</sub> H <sub>5</sub>
11	Acetyl-His	i-amyl	-C <sub>6</sub> H <sub>5</sub>
12	Acetyl-Thr	i-amyl	-C <sub>6</sub> H <sub>5</sub>
13	Acetyl-NHCH(C(CH <sub>3</sub> ) <sub>2</sub> (SCH <sub>3</sub> ))C(O)-	i-amyl	-C <sub>6</sub> H <sub>5</sub>
14	Cbz-Asn	i-amyl	-C <sub>6</sub> H <sub>5</sub>
15	Cbz-Ala	i-amyl	-C <sub>6</sub> H <sub>5</sub>
16	(N,N-dimethylglyciny)Val	i-amyl	-C <sub>6</sub> H <sub>5</sub>
17	(N-methylglyciny)Val	i-amyl	-C <sub>6</sub> H <sub>5</sub>
18	(N,N-dimethylglyciny)Ile	i-amyl	-C <sub>6</sub> H <sub>5</sub>
19	(N-methylglyciny)Ile	i-amyl	-C <sub>6</sub> H <sub>5</sub>

TABLE 5 (Cont'd)









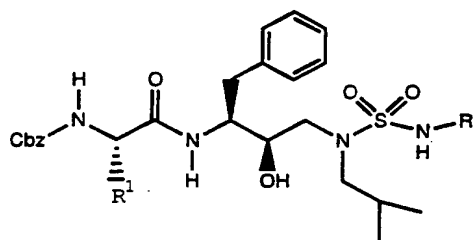
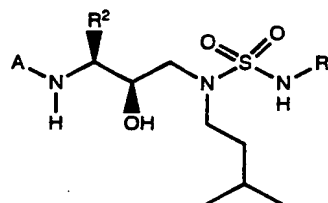
Entry	A	R <sup>3</sup>	R <sup>4</sup>
20	(N,N-dimethylglyciny1)Val	i-butyl	n-butyl
21	(N,N-dimethylglyciny1)Val	i-amyl	n-butyl
22	(N,N-dimethylglyciny1)Val		n-butyl
23	(N,N-dimethylglyciny1)Val	CH <sub>2</sub> - 	n-butyl
24	(N,N-dimethylglyciny1)Ile	i-butyl	n-butyl
25	(N,N-dimethylglyciny1)Ile	i-amyl	n-butyl
26	(N,N-dimethylglyciny1)Ile		n-butyl
27	(N,N-dimethylglyciny1)Ile	CH <sub>2</sub> - 	n-butyl
20	Cbz-Ala	i-amyl	-C <sub>6</sub> H <sub>5</sub>
21	Cbz-beta-cyanoAla	i-amyl	-C <sub>6</sub> H <sub>5</sub>
22	Cbz-t-BuGly	i-amyl	-C <sub>6</sub> H <sub>5</sub>
23	Q-t-BuGly	i-amyl	-C <sub>6</sub> H <sub>5</sub>
24	Q-SCH <sub>3</sub> Cys	i-amyl	-C <sub>6</sub> H <sub>5</sub>
25	Cbz-SCH <sub>3</sub> Cys	i-amyl	-C <sub>6</sub> H <sub>5</sub>
26	Q-Asp	i-amyl	-C <sub>6</sub> H <sub>5</sub>
27	Cbz-(NHCH(C(CH <sub>3</sub> ) <sub>2</sub> (SCH <sub>3</sub> ))C(O)-	i-amyl	-C <sub>6</sub> H <sub>5</sub>
28	Cbz-EtGly	i-amyl	-C <sub>6</sub> H <sub>5</sub>
29	Cbz-PrGly	i-amyl	-C <sub>6</sub> H <sub>5</sub>
30	Cbz-Thr	i-amyl	-C <sub>6</sub> H <sub>5</sub>
31	Q-Phe	i-amyl	-C <sub>6</sub> H <sub>5</sub>
32	Cbz-Phe	i-amyl	-C <sub>6</sub> H <sub>5</sub>
33	(N,N-dimethylglyciny1)Val	i-butyl	t-butyl
34	(N,N-dimethylglyciny1)Val	i-amyl	t-butyl
35	(N,N-dimethylglyciny1)Val		t-butyl
36	(N,N-dimethylglyciny1)Val	CH <sub>2</sub> - 	t-butyl
37	(N,N-dimethylglyciny1)Ile	i-butyl	t-butyl
38	(N,N-dimethylglyciny1)Ile	i-amyl	t-butyl
39	(N,N-dimethylglyciny1)Ile		t-butyl
40	(N,N-dimethylglyciny1)Ile	CH <sub>2</sub> - 	t-butyl

TABLE 6



Entry	R <sup>1</sup>	R <sup>4</sup>
1	CH <sub>2</sub> SO <sub>2</sub> CH <sub>3</sub>	t-butyl
2	(R) -CH(OH)CH <sub>3</sub>	t-butyl
3	CH(CH <sub>3</sub> ) <sub>2</sub>	t-butyl
4	(R, S)CH <sub>2</sub> SOCH <sub>3</sub>	t-butyl
5	CH <sub>2</sub> SO <sub>2</sub> NH <sub>2</sub>	t-butyl
6	CH <sub>2</sub> SCH <sub>3</sub>	t-butyl
7	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	t-butyl
8	CH <sub>2</sub> CH <sub>2</sub> C(O)NH <sub>2</sub>	t-butyl
9	(S) -CH(OH)CH <sub>3</sub>	t-butyl
10	-CH <sub>2</sub> C≡C-H	t-butyl

TABLE 7



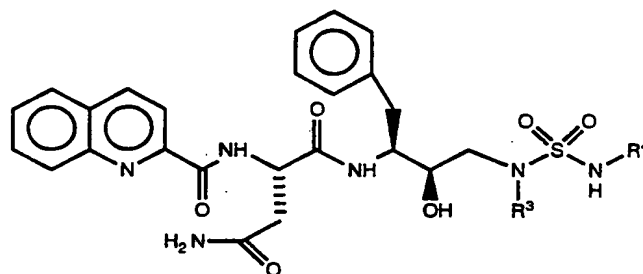
Entry	R <sup>2</sup>	A	R <sup>4</sup>
1	n-Bu	Cbz-Asn	t-butyl
2	cyclohexylmethyl	Cbz-Asn	t-butyl
3	n-Bu	Boc	t-butyl
4	n-Bu	Cbz	t-butyl
5	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	Boc	t-butyl
6	P-F-C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	Cbz	t-butyl
7	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	benzoyl	t-butyl
8	cyclohexylmethyl	Cbz	t-butyl
9	n-Bu	Q-Asn	t-butyl
10	cyclohexylmethyl	Q-Asn	t-butyl
11	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	Cbz-Ile	t-butyl
12	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	Q-Ile	t-butyl
13	P-F-C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	Cbz-t-BuGly	t-butyl
14	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	Q-t-BuGly	t-butyl
15	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	Cbz-Val	t-butyl
16	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	Q-Val	t-butyl
17	2-naphthylmethyl	Cbz-Asn	t-butyl
18	2-naphthylmethyl	Q-Asn	t-butyl
19	2-naphthylmethyl	Cbz	t-butyl
20	n-Bu	Cbz-Val	t-butyl
21	n-Bu	Q-Val	t-butyl
22	n-Bu	Q-Ile	t-butyl
23	n-Bu	Cbz-t-BuGly	t-butyl

TABLE 7 (Cont'd)

Entry	R <sup>2</sup>	A	R <sup>4</sup>
24	n-Bu	Q-t-BuGly	t-butyl
25	p-F(C <sub>6</sub> H <sub>4</sub> )CH <sub>2</sub>	Q-Asn	t-butyl
26	p-F(C <sub>6</sub> H <sub>4</sub> )CH <sub>2</sub>	Cbz	t-butyl
27	p-F(C <sub>6</sub> H <sub>4</sub> )CH <sub>2</sub>	Cbz-Asn	t-butyl
28	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	Cbz-propargylglycine	t-butyl
29	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	Q-propargylglycine	t-butyl
30	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	acetylpropargylglycine	t-butyl



TABLE 8



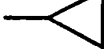
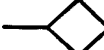
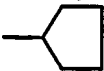
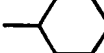
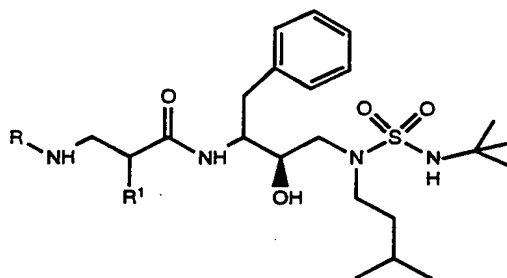
Entry	R <sup>3</sup>	R <sup>4</sup>
1	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C(CH <sub>3</sub> ) <sub>2</sub>
2	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	
3	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	
4	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	
5	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	

TABLE 9



Entry	R	R <sup>1</sup>
1		-CH <sub>3</sub>
2		-CH <sub>3</sub>
3		-CH(CH <sub>3</sub> ) <sub>2</sub>
4		-CH(CH <sub>3</sub> ) <sub>2</sub>
5		-C(CH <sub>3</sub> ) <sub>3</sub>
6		-CH <sub>3</sub>
7		-CH <sub>3</sub>

Table 9 (Cont'd)

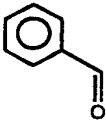
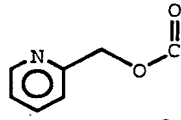
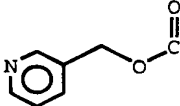
Entry	R	R <sup>1</sup>
8	$\text{HO}_2\text{CCH}_2\text{CH}_2\text{C}(=\text{O})-$	-CH <sub>3</sub>
9		-CH <sub>3</sub>
10	$\text{CH}_3\text{NH-C}(=\text{O})-$	-CH <sub>3</sub>
11	$(\text{CH}_3)_2\text{CH-C}(=\text{O})-$	-CH <sub>3</sub>
12	$\text{CH}_3\text{OCH}_2\text{C}(=\text{O})-$	-CH <sub>3</sub>
13	$(\text{CH}_3)_2\text{NCH}_2\text{C}(=\text{O})-$	-CH <sub>3</sub>
14	$\text{CH}_3\text{CH}(\text{OH})\text{C}(=\text{O})-$	-CH <sub>3</sub>
15		-CH <sub>3</sub>
16		-CH <sub>3</sub>

TABLE 9 (Cont'd)

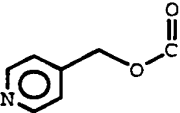
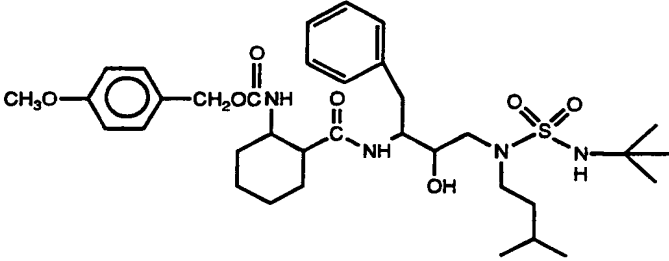
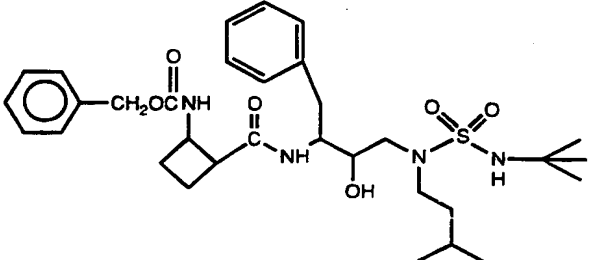
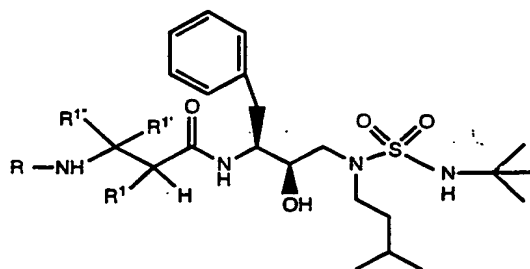
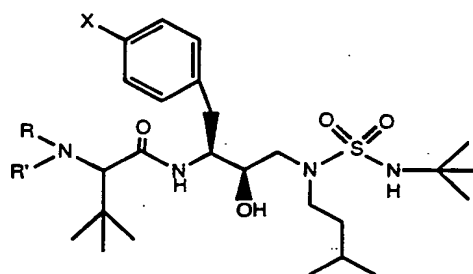
Entry	R	R <sup>1</sup>
17		-CH <sub>3</sub>
18		
19		

TABLE 10



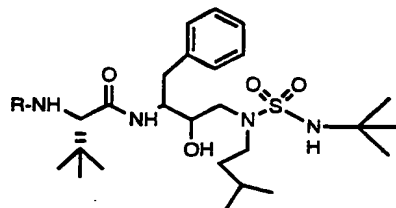
Entry	R <sup>1</sup>	R <sup>1'</sup>	R <sup>1''</sup>	R
1	H	H	H	
2	H	H	H	
3	H	CH <sub>3</sub>	H	
4	H	CH <sub>3</sub>	CH <sub>3</sub>	
5	H	H	CO <sub>2</sub> CH <sub>3</sub>	
6	H	H	H	
7	H	H	H	
8	H	H	CONH <sub>2</sub>	Cbz
9	H	H	CONH <sub>2</sub>	2-quinolinylcarbonyl

TABLE 11



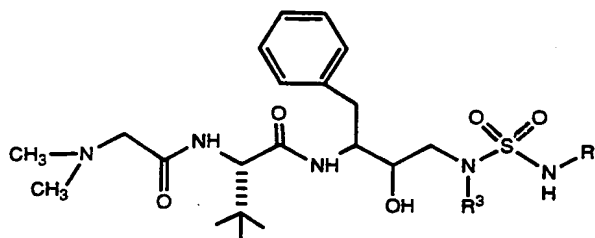
Entry	R	R'	X
1	R=H	R'=H	X=H
2	R=Me	R'=Me	X=H
3	R=H	R'=Me	X=H
4	R=Me	R'=Me	X=F
5	R=H	R'=Me	X=F
6	R=Cbz	R'=Me	X=H
7	R=H	R'=Bz	X=H
8	R+R'=pyrrolle		X=H

TABLE 12



Entry	Acyl Group (R)
1	benzyloxycarbonyl
2	<u>tert</u> -butoxycarbonyl
3	acetyl
4	2-quinoylcarbonyl
5	phenoxyacetyl
6	benzoyl
7	methyloxaloyl
8	pivaloyl
9	trifluoracetyl
10	bromoacetyl
11	hydroxyacetyl
12	morpholinylacetyl
13	N,N-dimethylaminoacetyl
14	N-benzylaminoacetyl
15	N-phenylaminoacetyl
16	N-benzyl-N-methylaminoacetyl
17	N-methyl-N-(2-hydroxyethyl)aminoacetyl
18	N-methylcarbamoyl
19	3-methylbutyryl
20	N-isobutylcarbamoyl
21	succinoyl (3-carboxypropionyl)
22	carbamoyl
23	N-(2-indanyl)aminoacetyl
24	N-methylaminoacetyl

TABLE 13



Entry	R <sup>3</sup>	R <sup>4</sup>
1	-CH <sub>3</sub>	-n-Butyl
2	-n-Butyl	-CH <sub>3</sub>
3	-i-Butyl	-n-Butyl
4	-i-Propyl	-n-Butyl
5	-C <sub>6</sub> H <sub>5</sub>	-n-Butyl
6	-CH <sub>2</sub> -	-n-Butyl
7	-CH <sub>2</sub> -	-n-Butyl
8	-	-n-Butyl
9	-i-Butyl	-n-Propyl
10	-i-Butyl	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>
11	-(R)-CH(CH <sub>3</sub> )-	-n-Butyl
12	-CH <sub>2</sub> -	-i-Propyl
13	-CH <sub>2</sub> -	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>
14	i-Butyl	-CH <sub>2</sub> CH <sub>3</sub>
15	i-Butyl	-CH(CH <sub>3</sub> ) <sub>2</sub>
16	i-Butyl	-



TABLE 13 (Cont'd)








Entry	R <sup>3</sup>	R <sup>4</sup>
17	-CH <sub>2</sub> - 	-(CH <sub>2</sub> ) <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>
18	(CH <sub>2</sub> ) <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-CH(CH <sub>3</sub> ) <sub>2</sub>
19	i-Butyl	-CH(CH <sub>3</sub> ) <sub>2</sub>
20	i-Butyl	-C(CH <sub>3</sub> ) <sub>3</sub>
21	-CH <sub>2</sub> - 	-C(CH <sub>3</sub> ) <sub>3</sub>
22	-(CH <sub>2</sub> ) <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C(CH <sub>3</sub> ) <sub>3</sub>
23	-CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	-C(CH <sub>3</sub> ) <sub>3</sub>
24	-(CH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	-C(CH <sub>3</sub> ) <sub>3</sub>
25	n-Butyl	-C(CH <sub>3</sub> ) <sub>3</sub>
26	n-Pentyl	-C(CH <sub>3</sub> ) <sub>3</sub>
27	n-Hexyl	-C(CH <sub>3</sub> ) <sub>3</sub>
28	-CH <sub>2</sub> - 	-C(CH <sub>3</sub> ) <sub>3</sub>
29	-CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>	-C(CH <sub>3</sub> ) <sub>3</sub>
30	-CH <sub>2</sub> CH <sub>2</sub> -N 	-C(CH <sub>3</sub> ) <sub>3</sub>
31	-CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> OCH <sub>3</sub> (para)	-C(CH <sub>3</sub> ) <sub>2</sub>
32	-CH <sub>2</sub> - 	-C(CH <sub>3</sub> ) <sub>3</sub>
33	-CH <sub>2</sub> - 	-C(CH <sub>3</sub> ) <sub>3</sub>
34	-(CH <sub>2</sub> ) <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>	-C(CH <sub>3</sub> ) <sub>3</sub>
35	-(CH <sub>2</sub> ) <sub>4</sub> OH	-C(CH <sub>3</sub> ) <sub>3</sub>
36	-CH <sub>2</sub> - 	-C(CH <sub>3</sub> ) <sub>3</sub>

TABLE 13 (Cont'd)












Entry	R <sup>3</sup>	R <sup>4</sup>
37	-CH <sub>2</sub> - 	-C(CH <sub>3</sub> ) <sub>3</sub>
38	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-C <sub>6</sub> H <sub>5</sub>
39	i-amyl	-CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>
40		-CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>
41	CH <sub>3</sub> - 	-CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>
42	i-butyl	-CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>
43	-CH <sub>2</sub> Ph	-Ph
44	-CH <sub>2</sub> - 	-Ph
45	-CH <sub>2</sub> - 	-Ph
46	-CH <sub>2</sub> - 	-Ph
47	-CH <sub>2</sub> - 	-Ph
48	-CH <sub>2</sub> - 	-Ph
49	-CH <sub>2</sub> CH=CH <sub>2</sub>	-Ph
50	- 	-Ph
51		-Ph
52	-CH <sub>2</sub> CH <sub>2</sub> Ph	-Ph
53	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	-Ph
54	-CH <sub>2</sub> CH <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	-Ph
55	-CH <sub>2</sub> CH <sub>2</sub> -N 	-Ph
56	-CH <sub>3</sub>	-Ph

TABLE 13 (Cont'd)
























Entry	R <sup>3</sup>	R <sup>4</sup>
57	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> SCH <sub>3</sub>	-Ph
58	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> S(O) <sub>2</sub> CH <sub>3</sub>	-Ph
59	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	- 
60	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-CH <sub>2</sub> - 
61	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
62	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-CH <sub>3</sub>
63	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-  -F
64	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	- 
65	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-  -NO <sub>2</sub>
66	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	- 
67	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-  -OCH <sub>3</sub>
68	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-  -NO <sub>2</sub>
69	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-  -NO <sub>2</sub>
70	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-  -CF <sub>3</sub>
71	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-  -NHAc
72	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-  -Cl

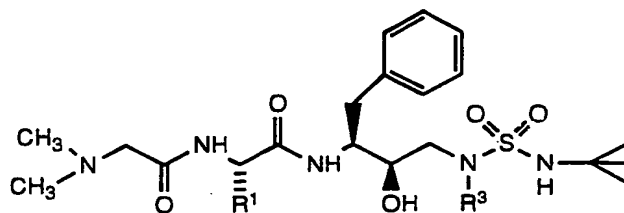
TABLE 13 (Cont'd)

Entry	R <sup>3</sup>	R <sup>4</sup>
73	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-  -CH <sub>3</sub>
74	-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-  -CH <sub>3</sub>
75	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	- 
76	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-  -F
77	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-  -NHAc
78	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-  -CH <sub>3</sub>
79	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	-  -OCH <sub>3</sub>
80	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	-  -OCH <sub>3</sub>
81	i-butyl	t-butyl
82	i-amyl	t-butyl
83	- 	t-butyl
84	-CH <sub>2</sub> - 	t-butyl
85	i-butyl	- 

a benzyloxycarbonyl

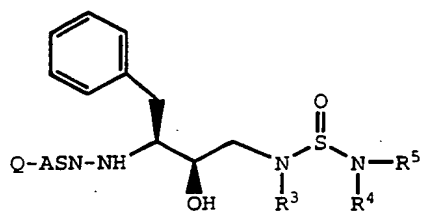
b 2-quinolinylcarbonyl

Table 14



Entry	R <sup>1</sup>	R <sup>3</sup>
1	C(CH <sub>3</sub> ) <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>
2	CH <sub>2</sub> C≡CH	CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>
3	C(CH <sub>3</sub> ) <sub>2</sub> (SCH <sub>3</sub> )	CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>
4	C(CH <sub>3</sub> ) <sub>2</sub> (S(O)CH <sub>3</sub> )	CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>
5	C(CH <sub>3</sub> ) <sub>2</sub> (S(O) <sub>2</sub> CH <sub>3</sub> )	CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>
6	C(CH <sub>3</sub> ) <sub>3</sub>	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>
7	C(CH <sub>3</sub> ) <sub>3</sub>	
8	CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>
9	CH(CH <sub>2</sub> CH <sub>3</sub> )(CH <sub>3</sub> )	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>

TABLE 15




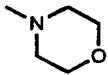
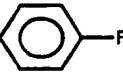


R <sub>3</sub>	
-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-N(CH <sub>3</sub> ) <sub>2</sub>
-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>
-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-N(CH(CH <sub>3</sub> ) <sub>2</sub> ) <sub>2</sub>
-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-N(CH <sub>3</sub> ) <sub>2</sub>
-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	-N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>
-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	
-CH <sub>2</sub> -  -F	-N(CH <sub>3</sub> ) <sub>2</sub>
	-N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>
-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	
-CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	

TABLE 15 (Cont'd.)

R <sub>3</sub>	$\begin{array}{c} \text{--- N --- R}_4 \\   \\ \text{R}_5 \end{array}$
	N(CH <sub>3</sub> ) (t-Bu)

TABLE 15 (Cont'd.)


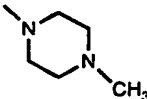
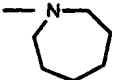
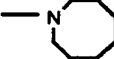

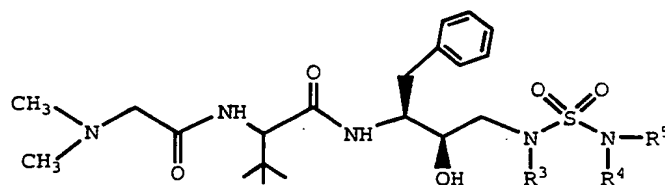
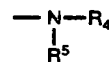
R <sub>3</sub>	$\begin{array}{c} \text{---N---R}_4 \\   \\ \text{R}_5 \end{array}$
$\text{---CH}_2\text{---}$ 	
$\text{---CH}_2\text{CH}(\text{CH}_3)_2$	
$\text{---CH}_2\text{CH}(\text{CH}_3)_2$	
$\text{---CH}_2\text{CH}(\text{CH}_3)_2$	



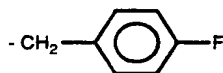
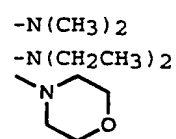
TABLE 16

R<sub>3</sub>

-CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>  
 -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>  
 -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>

-N(CH<sub>3</sub>)<sub>2</sub>  
 -N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>  
 -N(CH(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>

-CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>  
 -CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>  
 -CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>



-N(CH<sub>3</sub>)<sub>2</sub>  
 -N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>

TABLE 16 (Cont'd.)

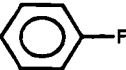

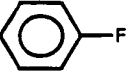

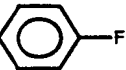
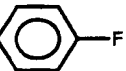
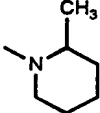
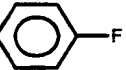
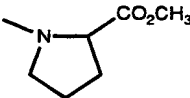
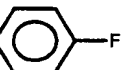
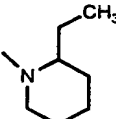
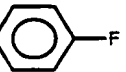
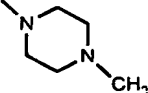
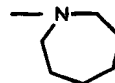
$R_3$	$\begin{array}{c} \text{---N---R}_4 \\   \\ \text{R}^5 \end{array}$
$\text{---CH}_2\text{---}$ 	
$\text{---CH}_2\text{---}$ 	
$\text{---CH}_2\text{---}$ 	$\text{N(CH}_3\text{) (t-Bu)}$
$\text{---CH}_2\text{---}$ 	
$\text{---CH}_2\text{---}$ 	
$\text{---CH}_2\text{---}$ 	
$\text{---CH}_2\text{---}$ 	

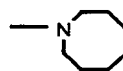
TABLE 16 (Cont'd.)

R <sub>3</sub>	
----------------	---

-CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>



-CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>



-CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>



Example 22

The compounds of the present invention are effective HIV protease inhibitors. Utilizing an enzyme assay as described below, the compounds set forth in the examples herein disclosed inhibited the HIV enzyme. The preferred compounds of the present invention and their calculated IC<sub>50</sub> (inhibiting concentration 50%, i.e., the concentration at which the inhibitor compound reduces enzyme activity by 50%) values are shown in Table 17. The enzyme method is described below. The substrate is 2-Ile-Nle-Phe(p-NO<sub>2</sub>)-Gln-ArgNH<sub>2</sub>. The positive control is MVT-101 (Miller, M. et al, Science, 246, 1149 (1989)). The assay conditions are as follows:

Assay buffer: 20 mM sodium phosphate, pH 6.4  
20% glycerol  
1 mM EDTA  
1 mM DTT  
0.1% CHAPS

The above described substrate is dissolved in DMSO, then diluted 10 fold in assay buffer. Final substrate concentration in the assay is 80  $\mu$ M.

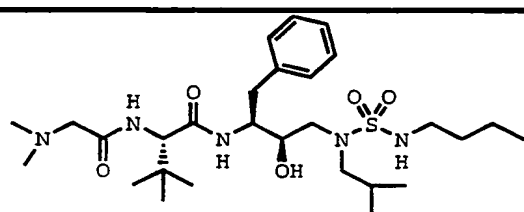
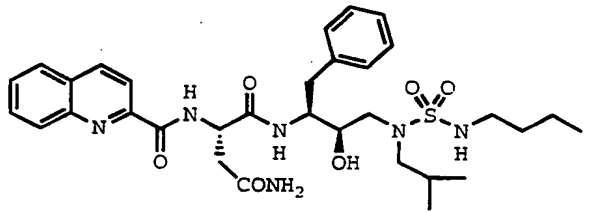
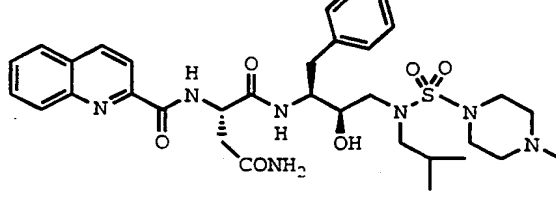
HIV protease is diluted in the assay buffer to a final enzyme concentration of 12.3 nanomolar, based on a molecular weight of 10,780.

The final concentration of DMSO is 14% and the final concentration of glycerol is 18%. The test compound is dissolved in DMSO and diluted in DMSO to 10x the test concentration; 10 $\mu$ l of the enzyme preparation is added, the materials mixed and then the mixture is incubated at ambient temperature for 15 minutes. The enzyme reaction is initiated by the addition of 40 $\mu$ l of

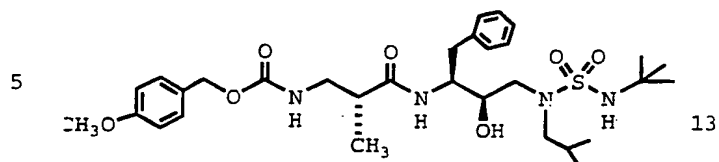
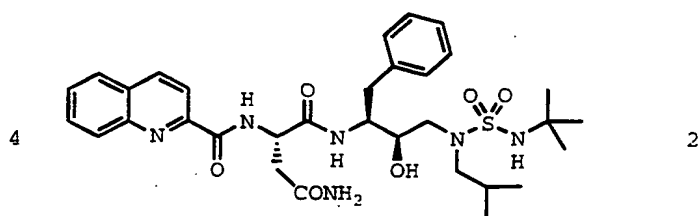
substrate. The increase in fluorescence is monitored at 4 time points (0, 8, 16 and 24 minutes) at ambient temperature. Each assay is carried out in duplicate wells.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

TABLE 17

Entry	Compound	IC <sub>50</sub> (nanomolar)
1		40
2		5
3		3

115



5

Example 23

10 The effectiveness of the compounds listed in Table 17 were determined in the above-described enzyme assay and in a CEM cell assay.

15 The HIV inhibition assay method of acutely infected cells is an automated tetrazolium based colorimetric assay essentially that reported by Pawles et al, J. Virol. Methods, 20, 309-321 (1988). Assays were performed in 96-well tissue culture plates. CEM cells, a CD4<sup>+</sup> cell line, were grown in RPMI-1640 medium (Gibco) supplemented with a 10% fetal calf serum and were

20 then treated with polybrene (2μg/ml). An 80 μl volume of medium containing 1 x 10<sup>4</sup> cells was dispensed into each well of the tissue culture plate. To each well was added a 100μl volume of test compound dissolved in tissue culture medium (or medium without test compound as a

25 control) to achieve the desired final concentration and

the cells were incubated at 37°C for 1 hour. A frozen culture of HIV-1 was diluted in culture medium to a concentration of  $5 \times 10^4$  TCID<sub>50</sub> per ml (TCID<sub>50</sub> = the dose of virus that infects 50% of cells in tissue culture), and a 20 $\mu$ L volume of the virus sample (containing 1000 TCID<sub>50</sub> of virus) was added to wells containing test compound and to wells containing only medium (infected control cells). Several wells received culture medium without virus (uninfected control cells). Likewise, the intrinsic toxicity of the test compound was determined by adding medium without virus to several wells containing test compound. In summary, the tissue culture plates contained the following experiments:

15

	Virus	Cells		Drug	
20	1.	+		-	-
	2.	+		+	-
	3.	+		-	+
	4.	+		+	+

25

In experiments 2 and 4 the final concentrations of test compounds were 1, 10, 100 and 500  $\mu$ g/ml. Either azidothymidine (AZT) or dideoxyinosine (ddI) was included as a positive drug control. Test compounds were dissolved in DMSO and diluted into tissue culture medium so that the final DMSO concentration did not exceed 1.5% in any case. DMSO was added to all control wells at an appropriate concentration.

30

Following the addition of virus, cells were incubated at 37°C in a humidified, 5% CO<sub>2</sub> atmosphere for 7 days. Test compounds could be added on days 0, 2 and 5 if desired. On day 7, post-infection, the cells in each well were resuspended and a 100 $\mu$ l sample of each cell

35

suspension was removed for assay. A 20 $\mu$ L volume of a 5 mg/ml solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was added to each 100 $\mu$ L cell suspension, and the cells were incubated for 4 hours at 27°C in a 5% CO<sub>2</sub> environment. During this incubation, MTT is metabolically reduced by living cells resulting in the production in the cell of a colored formazan product. To each sample was added 100 $\mu$ L of 10% sodium dodecylsulfate in 0.01 N HCl to lyse the cells, and samples were incubated overnight. The absorbance at 590 nm was determined for each sample using a Molecular Devices microplate reader. Absorbance values for each set of wells is compared to assess viral control infection, uninfected control cell response as well as test compound by cytotoxicity and antiviral efficacy.

The biological data shown in Tables 18 and 19 were obtained from the compounds shown in Tables 1C and 3B, respectively.



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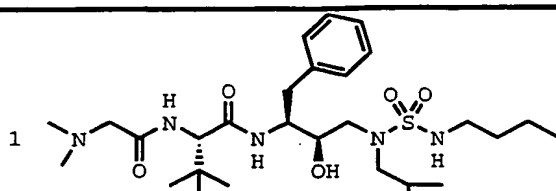
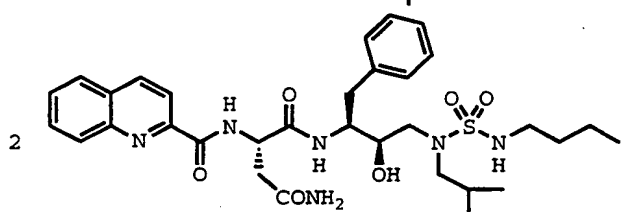
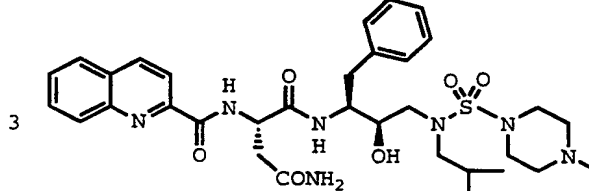
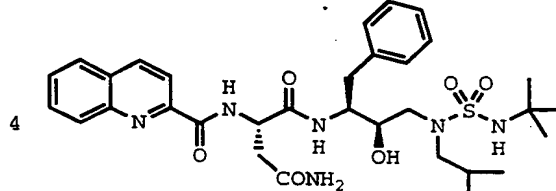
TABLE 18

	Entry Table 1C	IC <sub>50</sub> or % Inhibition	EC <sub>50</sub>	TD <sub>50</sub>
5	A	29% @ 0.1 $\mu$ M		
	B	55% @ 10.0 $\mu$ M		
10	C	59% @ 1.0 $\mu$ M		
	D	29% @ 0.1 $\mu$ M		
15	E	70 nM	880 nM	7.5 $\mu$ M
	F	22% @ 0.1 $\mu$ M		
	G	66 nM		
20	H	48% @ 10.0 $\mu$ M		
	I	1.7 $\mu$ M		
25	J	2.69 $\mu$ M		
	K	60% @ 1.0 $\mu$ M		
	L	38% @ 10.0 $\mu$ M		
30				

TABLE 19

	Entry Table 3B	IC <sub>50</sub> (nM)	EC <sub>50</sub> (nM)	TD <sub>50</sub> ( $\mu$ M)
35	A	20		
40	B	27		
	C	42	350	>100
	D	4.4	27	289
45	E	4.0	13	8.3
	F	6.6	17	77

TABLE 20

Entry	Compound	IC <sub>50</sub> (nm)	EC <sub>50</sub> (nm)	TD <sub>50</sub> (nm)
1		40	167	56,000
2		5	23	65,000
3		3	42	28,000
4		2	<15	39,000

10

The compounds of the present invention are effective antiviral compounds and, in particular, are effective retroviral inhibitors as shown above. Thus, the subject compounds are effective HIV protease inhibitors.

15

It is contemplated that the subject compounds will also inhibit other retroviruses such as other lentiviruses in particular other strains of HIV, e.g. HIV-2, human T-cell leukemia virus, respiratory syncytial virus, simia

5 immunodeficiency virus, feline leukemia virus, feline immuno-deficiency virus, hepadnavirus, cytomegalovirus and picornavirus. Thus, the subject compounds are effective in the treatment and/or prophylaxis of retroviral infections.

10           Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or nonracemic mixtures thereof. The optical isomers can be obtained by resolution of the  
15 racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic  
20 acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the  
25 separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of Formula I with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be  
30 separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of Formula I can likewise be obtained by utilizing optically active starting materials.  
35 These isomers may be in the form of a free acid, a free base, an ester or a salt.

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, mesylate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

Total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001

to 50 mg/kg body weight daily and more usually 0.01 to 1 mg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

5           The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

10           The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of the  
15           disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part  
20           of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore may deviate from the preferred dosage regimen set forth above.

          The compounds of the present invention may be  
25           administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of  
30           transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

35           Injectable preparations, for example, sterile

injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may

include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, 5 emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

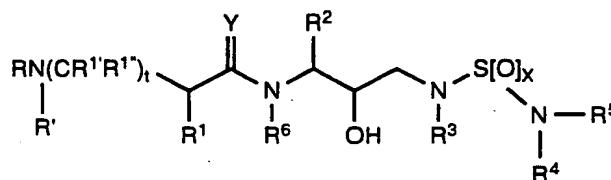
While the compounds of the invention can be administered as the sole active pharmaceutical agent, they 10 can also be used in combination with one or more immunomodulators, antiviral agents or other antiinfective agents. For example, the compounds of the invention can be administered in combination with AZT, DDI, DDV or with glucosidase inhibitors, such as N-butyl-1-deoxynojirimycin 15 or prodrugs thereof, for the prophylaxis and/or treatment of AIDS. When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single 20 composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are 25 obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

From the foregoing description, one skilled in 30 the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

WHAT IS CLAIMED IS:

1. A compound represented by the formula:



or a pharmaceutically acceptable salt, prodrug or ester thereof wherein:

- 10 R represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, alkoxycarbonyl, aryloxyalkyl, heteroaryloxyalkyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, 15 aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocycliloxy carbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, alkoxyalkyl, hydroxyalkyl, 20 aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, 25 heterocycloalkyl radicals, or wherein said aminocarbonyl and aminoalkanoyl radicals are disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

30 R' represents hydrogen and radicals as defined for R<sup>3</sup> or R"SO<sub>2</sub>- wherein R" represents radicals as defined for R<sup>3</sup>;



or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

- 5 R<sup>1</sup> represents hydrogen, -CH<sub>2</sub>SO<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>, -CO<sub>2</sub>CH<sub>3</sub>,  
-CONH<sub>2</sub>, -CH<sub>2</sub>C(O)NHCH<sub>3</sub>, -C(CH<sub>3</sub>)<sub>2</sub>(SH), -C(CH<sub>3</sub>)<sub>2</sub>(SCH<sub>3</sub>),  
-C(CH<sub>3</sub>)<sub>2</sub>(S(O)CH<sub>3</sub>), -C(CH<sub>3</sub>)<sub>2</sub>(S(O)<sub>2</sub>CH<sub>3</sub>), alkyl, haloalkyl,  
10 alkenyl, alkynyl and cycloalkyl radicals, and amino acid  
side chains selected from asparagine, S-methyl cysteine  
and methionine and the sulfoxide (SO) and sulfone (SO<sub>2</sub>)  
derivatives thereof, isoleucine, allo-isoleucine,  
alanine, leucine, tert-leucine, phenylalanine, ornithine,  
histidine, norleucine, glutamine, threonine, glycine,  
allo-threonine, serine, O-alkyl serine, aspartic acid,  
15 beta-cyano alanine and valine side chains;

- R<sup>1'</sup> and R<sup>1''</sup> independently represent hydrogen and radicals  
as defined for R<sup>1</sup>, or one of R<sup>1'</sup> and R<sup>1''</sup>, together with  
R<sup>1</sup> and the carbon atoms to which R<sup>1</sup>, R<sup>1'</sup> and R<sup>1''</sup> are  
20 attached, represent a cycloalkyl radical;

- R<sup>2</sup> represents alkyl, aryl, cycloalkyl, cycloalkylalkyl  
and aralkyl radicals, which radicals are optionally  
substituted with a group selected from alkyl and halogen  
25 radicals, -NO<sub>2</sub>, -C≡N, CF<sub>3</sub>, -OR<sup>9</sup>, -SR<sup>9</sup>, wherein R<sup>9</sup>  
represents hydrogen and alkyl radicals;

- R<sup>3</sup> represents alkyl, haloalkyl, alkenyl, alkynyl,  
hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl,  
30 heterocycloalkyl, heteroaryl, heterocycloalkylalkyl,  
aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and  
disubstituted aminoalkyl radicals, wherein said  
substituents are selected from alkyl, aryl, aralkyl,  
cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl,  
35 heterocycloalkyl, and heterocycloalkylalkyl radicals, or  
in the case of a disubstituted aminoalkyl radical, said

substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone or sulfoxide derivatives thereof;

R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen and radicals as defined by R<sup>3</sup> or together with a nitrogen atom to which they are bonded form a heterocycloalkyl or a heteroaryl radical;

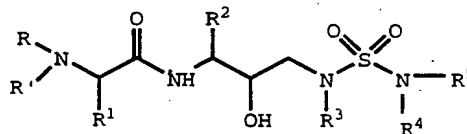
R<sup>6</sup> represents hydrogen and alkyl radicals;

x represents 1 or 2;

t represents either 0, 1 or 2; and

Y represents O, S and NR<sup>15</sup> wherein R<sup>15</sup> represents hydrogen and radicals as defined for R<sup>3</sup>.

2. Compound represented by the formula:



wherein:

R represents hydrogen, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, alkoxyalkyl, hydroxyalkyl, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl,

heterocyclylalkoxycarbonyl, heteroaralkancyl,  
heteroaralkoxycarbonyl, heteroaryloxycarbonyl,  
heteroaroyl, aminocarbonyl, aminoalkanoyl, and mono- and  
disubstituted aminocarbonyl and mono- and disubstituted  
5 aminoalkanoyl radicals wherein the substituents are  
selected from alkyl, aryl, aralkyl, cycloalkyl,  
cycloalkylalkyl, heteroaryl, heteroaralkyl,  
heterocycloalkyl, heterocycloalkylalkyl radicals, or where  
said aminoalkanoyl radical is disubstituted, said  
10 substituents along with the nitrogen atom to which they  
are attached form a heterocycloalkyl or heteroaryl  
radical;

R' represents hydrogen and radicals as defined for R<sup>3</sup> or  
15 R and R' together with the nitrogen to which they are  
attached represent heterocycloalkyl and heteroaryl  
radical;

R<sup>1</sup> represents hydrogen, -CH<sub>2</sub>SO<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>, -CO<sub>2</sub>CH<sub>3</sub>,  
20 -CONH<sub>2</sub>, -CH<sub>2</sub>C(O)NHCH<sub>3</sub>, -C(CH<sub>3</sub>)<sub>2</sub>(SH), -C(CH<sub>3</sub>)<sub>2</sub>(SCH<sub>3</sub>),  
-C(CH<sub>3</sub>)<sub>2</sub>(S[O]CH<sub>3</sub>), -C(CH<sub>3</sub>)<sub>2</sub>(S[O]<sub>2</sub>CH<sub>3</sub>), alkyl, haloalkyl,  
alkenyl, alkynyl and cycloalkyl radicals, and amino acid  
side chains selected from asparagine, S-methyl cysteine  
and methionine and the sulfoxide (SO) and sulfone (SO<sub>2</sub>)  
25 derivatives thereof, isoleucine, allo-isoleucine,  
alanine, leucine, tert-leucine, phenylalanine, ornithine,  
histidine, norleucine, glutamine, threonine, glycine,  
allo-threonine, serine, O-methyl serine, aspartic acid,  
beta-cyanoalanine and valine side chains;

30 R<sup>2</sup> represents alkyl, aryl, cycloalkyl, cycloalkylalkyl  
and aralkyl radicals, which radicals are optionally  
substituted with a group selected from alkyl and halogen  
radicals, -NO<sub>2</sub>, -C≡N, CF<sub>3</sub>, -OR<sup>9</sup>, -SR<sup>9</sup>, wherein R<sup>9</sup>  
35 represents hydrogen and alkyl radicals;

R<sup>3</sup> represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and  
5 disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said  
10 substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone or sulfoxide derivatives thereof;

15 R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen and radicals as defined by R<sup>3</sup>, or together with the nitrogen atom to which they are bonded represent heterocycloalkyl and heteroaryl radicals.

20 3. Compound of Claim 2 wherein R represents aralkoxycarbonyl and heteroaroyl radicals.

25 4. Compound of Claim 2 wherein R represents carbobenzoyl, 2-benzofurancarbonyl and 2-quinolinylcarbonyl radicals.

30 5. Compound of Claim 2 where R represents acetyl, N,N-dimethylaminoacetyl, N-methylaminoacetyl or N-benzyl-N-methylaminoacetyl.

35 6. Compound of Claim 2 wherein R<sup>1</sup> represents alkyl, alkynyl and alkenyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, threonine, allo-threonine, isoleucine, S-methyl

cysteine and the sulfone and sulfoxide derivatives thereof, alanine, and allo-isoleucine.

7. Compound of Claim 2 wherein R<sup>1</sup> represents  
5 methyl, propargyl, t-butyl, isopropyl and sec-butyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, S-methyl cysteine, allo-iso-leucine, iso-leucine, threonine, serine, aspartic acid, beta-cyano alanine, and allo-  
10 threonine side chains.

8. Compound of Claim 2 wherein R<sup>2</sup> represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals  
15 and radicals represented by the formula -OR<sup>9</sup> and -SR<sup>9</sup> wherein R<sup>9</sup> represents hydrogen and alkyl radicals.

9. Compound of Claim 2 wherein R<sup>2</sup> represents alkyl, cycloalkylalkyl and aralkyl radicals.  
20

10. Compound of Claim 2 wherein R<sup>2</sup> represents CH<sub>3</sub>SCH<sub>2</sub>CH<sub>2</sub>-, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals.

11. Compound of Claim 2 wherein R<sup>3</sup> independently represents alkyl, haloalkyl, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl and heteroaralkyl radicals.  
25  
30

12. Compound of Claim 2 wherein R<sup>3</sup> represents alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals.  
35

13. Compound of Claim 2 wherein R<sup>3</sup> and R<sup>4</sup> independently represent alkyl, heterocycloalkyl and heterocycloalkylalkyl radicals.
- 5 14. Compound of Claim 2 wherein R<sup>3</sup> represents isobutyl, n-propyl, isopropyl, n-butyl, isoamyl, cyclohexyl, cyclohexylmethyl, benzyl and pyridylmethyl radicals.
- 10 15. Compound of Claim 2 wherein R<sup>3</sup> is an isobutyl, n-butyl or isoamyl radical and R<sup>4</sup> is a tertiary-butyl radical.
- 15 16. Compound of Claim 2 wherein R<sup>3</sup> is an isobutyl, n-butyl or isoamyl radical and R<sup>4</sup> is a phenyl radical.
- 20 17. Compound of Claim 2 wherein R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkyl and heterocycloalkylalkyl radicals.
- 25 18. Compound of Claim 2 wherein R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen, alkyl and aryl radicals.
- 30 19. Compound of Claim 2 wherein R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen, methyl, ethyl, isopropyl, n-butyl, t-butyl, 1,1-dimethylpropyl, cyclohexyl and phenyl radicals.
- 35 20. Compound of Claim 2 wherein R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are bonded form a heterocycloalkyl or heteroaryl radical.

21. Compound of Claim 2 wherein R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are bonded form a heterocycloalkyl or heteroaryl radical having from 4 to 8 ring members.

5

22. Compound of Claim 2 wherein R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are bonded form a pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl radical.

10

23. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

15

24. A pharmaceutical composition comprising a compound of Claim 2 and a pharmaceutically acceptable carrier.

20

25. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a composition of Claim 23.

25

26. Method of Claim 25 wherein the retroviral protease is HIV protease.

27. Method of treating a retroviral infection comprising administering an effective amount of a composition of Claim 23.

30

28. Method of Claim 27 wherein the retroviral infection is an HIV infection.

35

29. Method for treating AIDS comprising administering an effective amount of a composition of Claim 23.

30. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a composition of Claim 24.

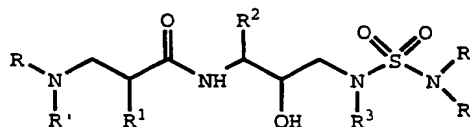
5 31. Method of Claim 30 wherein the retroviral protease is HIV protease.

32. Method of treating a retroviral infection comprising administering an effective amount of a  
10 composition of Claim 24.

33. Method of Claim 30 wherein the retroviral infection is an HIV infection.

15 34. Method for treating AIDS comprising administering an effective amount of a composition of Claim 24.

20 35. Compound represented by the formula:



wherein:

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl,  
25 alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl,  
30 heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, alkoxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and



- disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;
- R' represents hydrogen and radicals as defined for R<sup>3</sup> or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;
- R<sup>1</sup> represents hydrogen, -CH<sub>2</sub>SO<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -CH<sub>2</sub>C(O)NHCH<sub>3</sub>, -C(CH<sub>3</sub>)<sub>2</sub>(SH), -C(CH<sub>3</sub>)<sub>2</sub>(SCH<sub>3</sub>), -C(CH<sub>3</sub>)<sub>2</sub>(S[O]CH<sub>3</sub>), -C(CH<sub>3</sub>)<sub>2</sub>(S[O]<sub>2</sub>CH<sub>3</sub>), alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine and methionine and the sulfoxide (SO) and sulfone (SO<sub>2</sub>) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine, allo-threonine, serine, aspartic acid, beta-cyanoalanine and valine side chains;
- R<sup>2</sup> represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, -NO<sub>2</sub>, -C≡N, CF<sub>3</sub>, -OR<sup>9</sup>, -SR<sup>9</sup>, wherein R<sup>9</sup> represents hydrogen and alkyl radicals;
- R<sup>3</sup> represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl,

aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone or sulfoxide derivatives thereof;

R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen and radicals as defined by R<sup>3</sup>, or together with the nitrogen atom to which they are bonded represent heterocycloalkyl and heteroaryl radicals.

36. Compound of Claim 35 wherein R<sup>1</sup> represents hydrogen, alkyl, alkenyl and alkynyl radicals.

37. Compound of Claim 35 wherein R<sup>1</sup> represents methyl, ethyl, isopropyl, propargyl and t-butyl radicals.

38. Compound of Claim 35 wherein R' is  
 hydrogen and R is  $\text{NH}_2\overset{\text{O}}{\parallel}\text{C}$  or  $\text{CH}_3\text{NH}-\overset{\text{O}}{\parallel}\text{C}-$ .

39. Compound of Claim 35 wherein R' is hydrogen and R represents acetyl, phenoxyacetyl, 2-naphthyloxy-carbonyl, benzyloxycarbonyl, p-methoxybenzyloxycarbonyl.

40. Compound of Claim 35 wherein R and R' are independently selected from methyl and phenethyl radicals.

41. Compound of Claim 35 wherein R<sup>2</sup> represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula -OR<sup>9</sup> and -SR<sup>9</sup> wherein R<sup>9</sup> represents hydrogen and alkyl radicals.

42. Compound of Claim 35 wherein R<sup>2</sup> represents alkyl, cycloalkylalkyl and aralkyl radicals.

43. Compound of Claim 35 wherein R<sup>2</sup> represents CH<sub>3</sub>SCH<sub>2</sub>CH<sub>2</sub>-, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals.

44. Compound of Claim 35 wherein R<sup>2</sup> represents benzyl, 4-fluorobenzyl, and 2-naphthylmethyl radicals.

45. Compound of Claim 35 wherein R<sup>3</sup> independently represents alkyl, haloalkyl, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl and heteroaralkyl radicals.

46. Compound of Claim 35 wherein R<sup>3</sup> represents alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals.

47. Compound of Claim 35 wherein R<sup>3</sup> and R<sup>4</sup> independently represent alkyl, heterocycloalkyl and heterocycloalkylalkyl radicals.

48. Compound of Claim 35 wherein R<sup>3</sup> represents isobutyl, n-propyl, isopropyl, n-butyl, isoamyl, cyclohexyl, cyclohexylmethyl, benzyl and pyridylmethyl radicals.

49. Compound of Claim 35 wherein R<sup>3</sup> is an isobutyl, n-butyl or t-butyl radical and R<sup>4</sup> is a t-butyl radical.
- 5 50. Compound of Claim 35 wherein R<sup>3</sup> is an isobutyl, n-butyl or isoamyl radical and R<sup>4</sup> is a phenyl radical.
- 10 51. Compound of Claim 35 wherein R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkyl and heterocycloalkylalkyl radicals.
- 15 52. Compound of Claim 35 wherein R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen, alkyl and aryl radicals.
- 20 53. Compound of Claim 35 wherein R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen, methyl, ethyl, isopropyl, n-butyl, cyclohexyl, t-butyl, 1,1-dimethylpropyl and phenyl radicals.
- 25 54. Compound of Claim 35 wherein R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are bonded form a heterocycloalkyl or heteroaryl radical.
- 30 55. Compound of Claim 35 wherein R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are bonded form a heterocycloalkyl or heteroaryl radical having from 4 to 8 ring members.
- 35 56. Compound of Claim 35 wherein R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are bonded form a pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl radical.

57. A pharmaceutical composition comprising a compound of Claim 35 and a pharmaceutically acceptable carrier.

5

58. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a composition of Claim 57.

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59. Method of Claim 58 wherein the retroviral protease is HIV protease.

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60. Method of treating a retroviral infection comprising administering an effective amount of a composition of Claim 57.

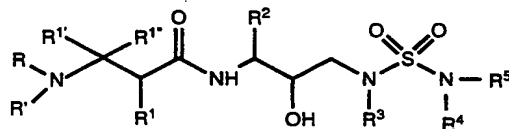
61. Method of Claim 60 wherein the retroviral infection is an HIV infection.

20

62. Method for treating AIDS comprising administering an effective amount of a composition of Claim 57.

25

63. Compound represented by the formula:



wherein:

R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl,

30

- heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, alkoxyalkyl,
- 5 hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl,
- 10 heterocycloalkyl, heterocycloalkylalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;
- 15 R' represents hydrogen and radicals as defined for R<sup>3</sup> or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;
- 20 R<sup>1</sup> represents hydrogen, -CH<sub>2</sub>SO<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -CH<sub>2</sub>C(O)NHCH<sub>3</sub>, -C(CH<sub>3</sub>)<sub>2</sub>(SH), -C(CH<sub>3</sub>)<sub>2</sub>(SCH<sub>3</sub>), -C(CH<sub>3</sub>)<sub>2</sub>(S[O]CH<sub>3</sub>), -C(CH<sub>3</sub>)<sub>2</sub>(S[O]<sub>2</sub>CH<sub>3</sub>), alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid
- 25 side chains selected from asparagine, S-methyl cysteine and methionine and the sulfoxide (SO) and sulfone (SO<sub>2</sub>) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine,
- 30 allo-threonine, serine, aspartic acid, beta-cyano alanine and valine side chains;
- R<sup>1</sup>' and R<sup>1</sup>" independently represent hydrogen and radicals as defined for R<sup>1</sup>, or one of R<sup>1</sup>' and R<sup>1</sup>", together with
- 35 R<sup>1</sup> and the carbon atoms to which R<sup>1</sup>, R<sup>1</sup>' and R<sup>1</sup>" are attached, represent a cycloalkyl radical;

R<sup>2</sup> represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, -NO<sub>2</sub>, -C≡N, CF<sub>3</sub>, -OR<sup>9</sup>, -SR<sup>9</sup>, wherein R<sup>9</sup>  
5 represents hydrogen and alkyl radicals;

R<sup>3</sup> represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl,  
10 aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or  
15 in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone or sulfoxide derivatives  
20 thereof;

R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen and radicals as defined by R<sup>3</sup>, or together with the nitrogen atom to which they are bonded represent heterocycloalkyl and  
25 heteroaryl radicals.

64. Compound of Claim 63 wherein R' represents hydrogen and R represents aralkoxycarbonyl and heteroaroyl radicals.  
30

65. Compound of Claim 63 wherein R' is hydrogen and R represents carbobenzoxy, 2-benzofurancarbonyl, and 2-quinolinylcarbonyl radicals.

35 66. Compound of Claim 63 wherein R' is hydrogen and R is 2-quinolinylcarbonyl.

67. Compound of Claim 63 wherein R<sup>1</sup>, R<sup>1'</sup> and R<sup>1''</sup> independently represent hydrogen and alkyl radicals having from 1 to about 4 carbon atoms, alkenyl, alkynyl, aralkyl radicals and radicals selected from -CH<sub>2</sub>SO<sub>2</sub>NH<sub>2</sub>, -CO<sub>2</sub>CH<sub>3</sub>, -CONHCH<sub>3</sub>, -CON(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>C(O)NHCH<sub>3</sub>, -CH<sub>2</sub>C(O)N(CH<sub>3</sub>)<sub>2</sub>, -CONH<sub>2</sub>, -C(CH<sub>3</sub>)<sub>2</sub>(SCH<sub>3</sub>), -C(CH<sub>3</sub>)<sub>2</sub>(S(O)CH<sub>3</sub>) and -C(CH<sub>3</sub>)<sub>2</sub>(S(O)CH<sub>3</sub>).

68. Compound of Claim 63 wherein R<sup>1</sup>, R<sup>1'</sup> and R<sup>1''</sup> independently represent hydrogen, methyl, ethyl, benzyl, phenylpropyl, propargyl, hydroxyl and radicals selected from -C(O)OCH<sub>3</sub>, -C(O)NH<sub>2</sub>, -C(O)OH.

69. Compound of Claim 63 wherein R<sup>1</sup> and R<sup>1'</sup> are both hydrogen and R<sup>1''</sup> is C(O)NH<sub>2</sub>.

70. Compound of Claim 63 wherein R represents aralkoxycarbonyl and heteroaroyl radicals.

71. Compound of Claim 63 wherein R<sup>1</sup> and R<sup>1'</sup> are both hydrogen and R<sup>1''</sup> is methyl.

72. Compound of Claim 63 wherein R<sup>1'</sup> is hydrogen and R<sup>1</sup> and R<sup>1''</sup> together with the carbon atoms to which they are attached form a three to six-membered cycloalkyl radical.

73. Compound of Claim 63 wherein R is carbobenzoy, 2-quinolinylcarbonyl and 2-benzofuran carbonyl radicals.

74. Compound of Claim 63 wherein R<sup>1</sup> and R<sup>1'</sup> are both hydrogen and R<sup>1''</sup> is propargyl.

75. Compound of Claim 63 wherein R<sup>2</sup> represents alkyl, cycloalkylalkyl and aralkyl radicals, which



radicals are optionally substituted with halogen radicals and radicals represented by the formula  $-CR^9$  and  $-SR^9$  wherein  $R^9$  represents hydrogen and alkyl radicals.

5                    76. Compound of Claim 63 wherein  $R^2$  represents alkyl, cycloalkylalkyl and aralkyl radicals.

                  77. Compound of Claim 63 wherein  $R^2$  represents aralkyl radicals.

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                  78. Compound of Claim 63 wherein  $R^3$  independently represents alkyl, haloalkyl, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl  
15 and heteroaralkyl radicals.

15

                  79. Compound of Claim 63 wherein  $R^3$  represents alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl  
20 radicals.

20

                  80. Compound of Claim 63 wherein  $R^3$  and  $R^4$  independently represent alkyl, heterocycloalkyl and heterocycloalkylalkyl radicals.

25

                  81. Compound of Claim 63 wherein  $R^3$  represents isobutyl, n-propyl, isopropyl, n-butyl, isoamyl, cyclohexyl, cyclohexylmethyl, benzyl and pyridylmethyl radicals.

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                  82. Compound of Claim 63 wherein  $R^3$  is an isobutyl, n-butyl or isoamyl radical and  $R^4$  is a tert-butyl radical.

83. Compound of Claim 63 wherein R<sup>3</sup> is an isobutyl, n-butyl or isoamyl radical and R<sup>4</sup> is a phenyl radical.

5           84. Compound of Claim 63 wherein R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkyl and heterocycloalkylalkyl radicals.

10           85. Compound of Claim 63 wherein R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen, alkyl and aryl radicals.

15           86. Compound of Claim 63 wherein R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen, methyl, ethyl, isopropyl, n-butyl, t-butyl, cyclohexyl, 1,1-dimethylpropyl and phenyl radicals.

20           87. Compound of Claim 63 wherein R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are bonded form a heterocycloalkyl or heteroaryl radical.

25           88. Compound of Claim 63 wherein R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are bonded form a heterocycloalkyl or heteroaryl radical having from 4 to 8 ring members.

30           89. Compound of Claim 63 wherein R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are bonded form a pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl radical.

35           90. A pharmaceutical composition comprising a compound of Claim 63 and a pharmaceutically acceptable carrier.

91. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a composition of Claim 89.

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92. Method of Claim 90 wherein the retroviral protease is HIV protease.

93. Method of treating a retroviral infection comprising administering an effective amount of a composition of Claim 89.

10

94. Method of Claim 92 wherein the retroviral infection is an HIV infection.

15

95. Method for treating AIDS comprising administering an effective amount of a composition of Claim 89.

20

96. A compound of Claim 1 which is:

N-[3-[[ (butylamino) sulfonyl] (2-methylpropyl) amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[[2-(dimethylamino)-1-oxoethyl]amino]dimethylbutanamide;

25

N-[3-[[ (methylamino) sulfonyl] (2-methylpropyl) amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[[2-(dimethylamino)-1-oxoethyl]amino]dimethylbutaneamide;

30

N1-[2R-hydroxy-3-[[ (4-methyl-1-piperazinyl) sulfonyl] (2-methylpropyl) amino]-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide;

35

N1-[3-[[ (butylamino) sulfonyl] (2-methylpropyl) amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide;

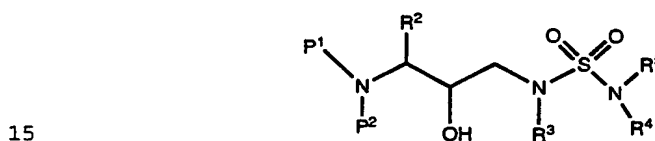
145

N1-[3-[[[(1,1-dimethylethyl)amino]sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide;

5 N'-[3-[[phenylamino]sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide; or

10 N'-[3-[[cyclohexylamino]sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide.

97. A compound represented by the formula:



wherein:

p1 and p2 independently represent hydrogen,  
 20 alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aryoyl, aryloxy carbonyl, aryloxy carbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxy carbonyl,  
 25 heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, alkoxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and  
 30 disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyl radicals, or where

said aminoalkanoyl radical is disubstituted said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

5

R<sup>2</sup> represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, -NO<sub>2</sub>, -C≡N, CF<sub>3</sub>, -OR<sup>9</sup>, -SR<sup>9</sup>, wherein R<sup>9</sup>

10 represents hydrogen and alkyl radicals;

R<sup>3</sup> represents hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl,

15 heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and

20 heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone  
25 or sulfoxide derivatives thereof;

R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen and radicals as defined by R<sup>3</sup> or together with a nitrogen atom to which they are bonded form a heterocycloalkyl or a  
30 heteroaryl radical.

98. Compound of Claim 97 wherein R<sup>3</sup> represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl,  
35 heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and

- disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or  
5 in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical; and
- 10 R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen and radicals as defined by R<sup>3</sup>, or together with the nitrogen atom to which they are bonded represent heterocycloalkyl and heteroaryl radicals.
- 15 99. A pharmaceutical composition comprising a compound of Claim 97 and a pharmaceutically acceptable carrier.
- 20 100. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a composition of Claim 99.
- 25 101. Method of Claim 100 wherein the retroviral protease is HIV protease.
102. Method of treating a retroviral infection comprising administering an effective amount of a composition of Claim 99.
- 30 103. Method of Claim 101 wherein the retroviral infection is an HIV infection.
- 35 104. Method for treating AIDS comprising administering an effective amount of a composition of Claim 99.

105. A compound of Claim 97 which is:

- phenylmethyl [2R-hydroxy-3-[[ (dimethylamino) sulfonyl] (2-methylpropyl) amino]-1S- (phenylmethyl) propyl] carbamate;
- 5 phenylmethyl [2R-hydroxy-3-[[ (dimethylamino) sulfonyl] (3-methylbutyl) amino]-1S- (phenylmethyl) propyl] carbamate;
- phenylmethyl [3-[[ (butylamino) sulfonyl] (2-methylpropyl) amino]-2R-hydroxy-1S- (phenylmethyl) propyl] carbamate;
- 10 phenylmethyl [2R-hydroxy-3-[[ (4-methyl-1-piperazinyl) sulfonyl] (2-methylpropyl) amino]-1S- (phenylmethyl) propyl] carbamate;
- 15 phenylmethyl [2R-hydroxy-3-[[ (1,1-dimethyl) amino] sulfonyl] (2-methylpropyl) amino]-1S- (phenylmethyl) propyl] carbamate;
- 20 phenylmethyl [2R-hydroxy-3-[[ (methylamino) sulfonyl] (2-methylpropyl) amino]-1S- (phenylmethyl) propyl] carbamate;
- phenylmethyl [2R-hydroxy-3-[[ (methylethyl) amino]-sulfonyl] (2-methylpropyl) amino]-1S- (phenylmethyl) propyl] carbamate;
- 25 phenylmethyl [2R-hydroxy-3-[[ (phenylamino) sulfonyl] (2-methylpropyl) amino]-1S- (phenylmethyl) propyl] carbamate;
- 30 phenylmethyl [2R-hydroxy-3-[[ (cyclohexylamino) sulfonyl] (2-methylpropyl) amino]-1S- (phenylmethyl) propyl] carbamate;
- or
- 35 phenylmethyl [2R-hydroxy-3-[[ (1-pyrrolidinyl) amino]-sulfonyl] (2-methylpropyl) amino]-1S- (phenylmethyl) propyl] carbamate.

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07C307/06 C07D295/22 C07K5/06 C07D215/48 A61K31/18  
A61K31/495 A61K31/45 A61K31/40 A61K37/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07C C07D C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,2 200 115 (SANDOZ) 27 July 1988 cited in the application see page 1 - page 5; examples 22-24,28 ----	1-24
X	EP,A,0 364 804 (ABBOTT LABORATORIES) 25 April 1990 see page 111, line 45 - page 112, line 29 ----	97,98
X	EP,A,0 468 641 (SHIONOGI) 29 January 1992 see pages 40-41, preparations 64,65 ----	97,98
A	WO,A,92 08699 (MONSANTO) 29 May 1992 see page 3 - page 5 -----	1-105

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance  
 "E" earlier document but published on or after the international filing date  
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
 "O" document referring to an oral disclosure, use, exhibition or other means  
 "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

17 January 1994

Date of mailing of the international search report

- 4. 02. 94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentaan 2  
 NL - 2220 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

ENGLISH, R



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 93/ 10552

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 25-34, 58-62, 91-95, 100-104 are directed to a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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